LIMITATIONS OF MEDICAL CARE ATTRIBUTABLE TO MEDICAL EDUCATION *

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IMPLICIT in this title are two assumptions: that the contemporary standard of medical care is deficient, and that to a significant degree the deficiencies are attributable to medical education.

Deficiencies of Medical Care

Deficiencies of care may be due to lack of knowledge, or to failure to apply existing knowledge; here we are concerned only with the latter. Failure to make full use of available medical knowledge may result from one or more of three causes:

1. Resources are inadequate, as they clearly are in underdeveloped countries.
2. Insufficient resources are allocated, as may be the case in developed countries.
3. Inefficient use is made of the resources which are allocated.

The first is an economic problem, and the second essentially a political one. Our concern here is with the third possibility—that there are deficiencies of medical care attributable primarily to the contemporary pattern of practice.

The inadequacy of the pattern of practice is most conspicuous in underdeveloped countries. It would be wrong, however, to suppose that the difficulties are restricted to distant places. Even where the technical resources of medicine are greatest there are problems, unsolved and probably insoluble within the traditional framework. The most important of them is the low standard of care provided for the mentally ill and chronic sick—the most serious deficiency of the medical services of the Western world. To some extent, no doubt, it could be relieved with more money, but this alone will not solve a problem which is rooted in the whole system of care which has evolved during the past two centuries.

Since the mentally ill and chronic sick occupy more than half of all hospital beds these deficiencies are already serious. They are likely to become more so in view of probable future trends. We are rapidly approaching a time when mortality between the end of the first month of life and the end of reproduction will be trivial—when almost all deaths will occur before or soon after birth and in late life. The most serious problems of morbidity will then be mental illness, and disease and disability associated with ageing. This pattern will be attributable in part to the age structure of the population, and in part to success with other causes of sickness and death. The outstanding problems with which medicine will be confronted are: prenatal mortality; mental illness; and sickness, disability, and mortality in late life. The contemporary pattern of medical practice is ill adapted to meet this situation.

The essential features of the existing medical services are: a curative service, based primarily on hospitals, with divided administration, staffing, and sometimes finance, of acute, chronic, and mental services; and a separate public-health service concerned with the prevention of disease. These features, it should be noted, are independent of the source of support; for example, they exist in Great Britain where all medical services are publicly financed, and in the United States, where public responsibility is more limited.

Hospitals

Many of the problems which confront the hospital service are rooted in the traditional separation of acute, mental, and chronic hospitals from one another. This subdivision does not correspond to the medical, nursing, and social needs of patients, and is wholly attributable to historical circumstances.

Each of the three major classes of patients presented to society at different times and as different problems. The object of the asylum was originally to protect the community from the supposed risks of the insane, and the methods adopted were penal in character. The object of the authorities concerned with relief of need was to make admission to an institution a condition of public assistance, and the foundation of hospitals was an unlooked-for complication of the decision to house the destitute. Until recently it was only in the general hospitals, which inherited the tradition of the voluntary hospitals, that investigation and treatment of disease were recognised as primary objects of institutional care. As a result the three systems were usually established on different sites and were financed, administered and staffed separately. Moreover, since hospitals were separated, they could not share common facilities, and each was conceived as a single building, providing a full range of services for selected patients.

These two features—the separation of the three classes of patients and the concept of the hospital as a single building—have serious disadvantages.

Mixing of patients with different needs.—Since segregation was not based on medical assessment, patients in each of the three types of hospital were heterogeneous in respect of need. Those in chronic-sick hospitals—the mentally defective, the psychotic, the senile, the infirm, the venereally infected, and the chronic sick of all ages—had in common only the fact that they were destitute. Those in mental hospitals exhibited the full range of mental and physical illness. Even in general hospitals, isolation from other facilities often made it necessary to retain patients not in need of hospital care, who were admitted, or kept after investigation and treatment, primarily for social reasons. And it is still true that the type of hospital to which a patient is admitted is determined, not by his medical needs, but according to whether his illness affects his mind or his body, and by his age.[1]

Artificial division of patients into acute and chronic classes.—The present distribution of services gives the impression that patients fall naturally into two classes according to whether they need short-term or long-term care. This results from the fact that, within a few weeks of admission, patients in general hospitals are expected to die, to get better, or to get out, whereas in mental and chronic hospitals duration of stay is often unnecessarily prolonged

*An address given at the Eighth Teaching Institute of the Association of American Medical Colleges at Hollywood Beach, Florida, on Nov. 2, 1960. It is published here by courtesy of the editor of the Proceedings of the Institute, which will form a volume entitled *Medical Services and Medical Education*.

1. McKeown, T., Mackintosh, J. M., Lowe, C. R. *Lancet*, 1961, i, 818.

because of inadequate services. It is not possible to say what, if services were adequate, the distribution of patients would be in respect of duration of stay, but certainly it would be much less conspicuously bimodal than it is today.

Difficulties of staffing.—In present circumstances it is impossible to attract enough doctors and nurses to mental and chronic hospitals, whose services are consequently far below the standard expected in acute hospitals. So long as the hospitals are isolated, they must depend on recruitment of staff prepared to devote themselves exclusively to these services, and the difficulties will remain. They can be overcome only by placing the hospitals close enough to the acute hospitals to make it possible for the same staff to serve both. This view rests on the belief that most doctors and nurses would be prepared to make a contribution to the care of the mentally ill and chronic sick, particularly if this obligation were acquired naturally in the course of training. They will not do so if it means cutting themselves off from their main interest.

Lack of flexibility.—Another disadvantage of divided hospitals is that they cannot respond readily to change in the size and character of the institutional population. For example, the isolation of hospitals for tuberculosis and other infectious diseases has made it much harder to transfer staff and buildings to alternative use when they are no longer required for their original purpose.

Reduplication of facilities.—Independent hospitals must provide a full range of services. Hence it is not possible to economise by pooling resources or to vary the design and equipment of buildings to make them complementary to one another.

Domiciliary Services

At present there are two conspicuous trends in the relationship of domiciliary and institutional services. They are towards isolation of the one from the other, and provision of all curative services from hospitals.

In many countries doctors are now engaged almost exclusively on either hospital or domiciliary work. This arrangement has many disadvantages, of which the most serious is perhaps that it restricts a logical development of services. For example, the mentally ill and aged sick cannot be divided simply into institutional and domiciliary classes; they require a complex pattern of care which would cut across traditional boundaries. Yet another disadvantage of separation is that doctors outside hospital tend to lose touch with the technical advances of medicine, whereas those inside, seeing only selected patients, may lose touch with reality.

The second significant trend is towards provision of all curative services from hospitals or clinics based on hospitals. Where there is no link between domiciliary and institutional work, and where the means of investigation and treatment are located in hospitals, this trend is almost irresistible. If health depended primarily on a battery of technical procedures there might be little regret in this change. As it does not, there is a strong case for preservation of a personal medical service.

Hence there are two grounds for retention of domiciliary practice intimately linked with the hospitals. In the first place it is needed for effective mobilisation of a wide range of services in which home, outpatient, and day care are at least as important as inpatient investigation and treatment. And secondly, it is essential for preservation of the personal character of the medical services.

Future Requirements

Let me now summarise again [2] the main features which should characterise the hospital if it is to avoid the disadvantages referred to above:

1. All types of patients should be cared for on a common site in approximately the proportions in which they occur in the institutional population.
2. The centre should consist of multiple buildings of varied size, design, equipment, and permanence of structure, each adapted to the needs of the class of patients to be admitted.
3. Patients should be classified strictly according to their medical, nursing, and other needs and placed in the unit most suitable for their care.
4. Medical and nursing services should be provided by a common staff.
5. The relationship of the hospital centre to the medical services of the community should be much more intimate than hitherto.

Two features of the hospital tradition would be abolished by the first four proposals—namely, the segregation of patients according to criteria (acute, mental, chronic) which do not correspond to their medical needs, and the concept of the hospital as a single independent building providing a full range of services. The fifth proposal would lead to a new relationship of hospital and domiciliary medical services.

The Public-Health Service

It is not difficult to see why the preventive and curative services became separated. In a period when the outstanding challenge was infectious disease, public authorities understandably established a public-health service dedicated to preventive measures. At first they were concerned only with environmental services, but their work was later extended into the field of personal care, though still limited essentially to prevention. This made prevention of disease a public responsibility and left a cure a private one. The separation has been retained even in countries such as Great Britain where all services are publicly financed.

In the circumstances in which they developed, the divided services were not inappropriate. Since the infections proved amenable to prevention, there was no anomaly in a public-health service directed exclusively to that end. Moreover, in the 19th century the curative services had little to offer. In both respects the situation has changed dramatically. The predominant problems are now prenatal mortality, mental illness, and the disease and disability of late life. In none of them can effective research or service be concerned exclusively with prevention or cure. Furthermore, resources for the treatment and care of patients with many forms of illness have improved considerably, and can be expected to improve much more in years to come.

If these conclusions are correct, we ought to get rid of the traditional division between preventive and curative medicine. In developed countries this can probably be done most readily by bringing all medical services concerned with the individual under a common administration and staff. Such an arrangement would place the division between personal medical care (all types) and the environmental services, rather than between preventive and curative medicine, as at present. It should not mean the end of medical interest in the environment; but in many countries the services have now reached a high level, at which they can be entrusted safely to the supervision of non-medical staff, advised when necessary by medical consultants.

2. McKeown, T. *Lancet*, 1958, i, 701.

Medical Education and Medical Care

We must now inquire to what extent deficiencies of care are attributable to medical education. I shall suggest that they are due largely to traditional restrictions of the responsibilities of teaching hospitals.

Restrictions of the Work of Teaching Centres

Selection of patients.—The patients admitted to teaching hospitals are highly selected, and this is excused on the grounds that selection is necessary for teaching and research. The basis of selection is determined essentially by the current interests of the staff and by accepting only short-term admissions: it virtually excludes the mentally ill and all long-term illness. Moreover, since patients are seen only in hospital, all that can be obtained from the teaching centre is a restricted view of the medical problems of a limited class of patients.

Methods.—With the predominant interest of teaching hospitals in the advance of knowledge, the methods exhibited are inevitably among the most complex, expensive, and time-consuming. Many of them are therefore inappropriate for the circumstances in which most graduates will find themselves.

Origin of the Restrictions

It is not difficult to understand how the restrictions arose: they have resulted from the grafting of the concept of scientific medicine on to the tradition of voluntary hospitals. From the time of its rebirth under secular auspices in the 18th century, the work of voluntary hospitals was sharply, and understandably, restricted. Those providing voluntary funds were entitled to decide what the charity was in aid of, and a medical staff receiving little or no remuneration could reasonably expect to dictate the nature of their work. Both interests coincided in agreement to leave to the State the intractable problems of mental illness, infectious disease, and all types of infirmity associated with destitution. Hence the Webbs' observation that the voluntary hospitals took what was interesting while the public hospitals were left with what was difficult.

The contrast between the interesting and the difficult was accentuated at teaching centres by the movement towards scientific medicine in which the Flexner report had so crucial a place. The unexceptionable wish to make medical schools centres of research led inevitably to selection of patients in respect of whom knowledge was advancing. They did not include the mentally ill or the chronic sick, who were thus removed from the vision of students and the minds of research-workers.

Disadvantages of the Restrictions

The traditional restrictions of the work of teaching hospitals have three serious disadvantages: one in the effect on medical education; another in respect of medical organisation; and a third in relation to medical research.

Medical education.—It is widely recognised that doctors acquire their concept of practice from their clinical teachers and that when they leave the teaching hospital they are determined to do the kind of work they saw as students. Since this excludes responsibility for large classes of patients, and is based on the most sophisticated methods, it provides an inadequate preparation for the realities of practice. The disadvantages, evident in developed countries in the standard of care of the mentally ill and chronic sick, reach grotesque proportions in underdeveloped countries.

Medical organisation.—Restricting their work as they do, teaching centres can make little contribution to study of the way in which medicine is to be organised. The form of the National Health Service in Great Britain, or indeed of the medical services of any country, owes little to ideas developed at teaching hospitals (or for that matter in university departments of public health). This deficiency becomes more obvious when we realise that patients cannot be divided simply into those ill enough to be admitted to a hospital bed and those well enough to remain at home, and that an effective service requires a complex pattern of practice.

In the care of the mentally ill, for example, it is now recognised that we need facilities for investigation and complex treatment, opportunities for re-training, occupational therapy and workshops, day hospitals, night care for patients who work in the community, and continued supervision from hospital of patients discharged home. It is here that the restrictions in teaching hospitals are so serious. By drawing their patients from a limited segment of the institutional population, and by restricting their activities to inpatient and traditional outpatient care, they can make no substantial contribution to the exploration of new and more effective forms of practice. It is a remarkable fact that the most farsighted services for the mentally ill in Great Britain are not to be found in teaching centres, but in one or two smaller provincial towns where a progressive hospital psychiatrist and medical officer of health have had the imagination and drive to overcome restrictions which tradition and, to some extent, the form of the service still impose.

Medical research.—A third disadvantage of the traditional restrictions is that in two ways they limit the scope of the research worker. In the first place they remove important diseases from his observation and experience; the slow progress with mental deficiency and schizophrenia must be due in part to their exclusion from teaching hospitals. Secondly, there is a large range of medical problems whose solution requires study of representative patients drawn from known populations. (In most teaching centres it is quite impossible to identify the population from which patients are derived.) The ætiology of congenital malformations, the causes of toxæmia of pregnancy and the nature of essential hypertension are examples of problems, in very different age periods, which have in common the requirement for a representative population as a basis of advance.

Proposals

My own belief is that staffs of teaching hospitals should accept a responsibility for exploring new patterns of practice, and thus put themselves into the forefront of thought about the future of medical organisation as well as of medical research. They should do this both because intellectually they have an important contribution to make, and because the demonstration of a modern concept of practice should be one of the first obligations of a teaching centre.

Perhaps the simplest way of creating the environment in which this can be done is to accept responsibility for all institutional services of an area, preferably the one in which the teaching hospital is placed. This in itself would be a tremendous advance, since it would ensure access to representative patients drawn from a known population. But we have also emphasised the advantages of breaking down the traditional barriers between institutional and domiciliary services and between preventive and curative medicine. For these purposes it would be desirable not to restrict the work of the teaching centre exclusively to

institutional care, and the ideal arrangement would be to make it responsible for all services in the defined area.

One important consequence of these changes would be that the work of teaching centres would vary considerably in different parts of the world, according to the problems of the country and its resources. One of the anomalies of contemporary medical education is that it aspires to a concept of "ideal practice" which is uniform and presupposes the existence of selected patients and unlimited resources. Whether these conditions exist anywhere is questionable; but in underdeveloped countries, which are attempting to pull themselves up by their own bootstraps, a system of education based on such assumptions can do little more than prepare doctors to use methods which are not available for the benefit of patients who do not exist.

We have emphasised also the advantages, in relation to research, of representative patients and a defined population. There are of course many problems which can be advanced only by study of the highly selected patients now admitted to teaching hospitals. There should be no difficulty in meeting both requirements. All that is needed is to make the size of the defined area such that numbers of representative patients drawn from it are in a reasonable relation to numbers of selected patients drawn from a much wider area for other research purposes.

Nothing in these proposals threatens the high level of technical excellence which teaching hospitals have always cherished. Recognition that the welfare of the mentally ill requires a far more comprehensive service than has hitherto been provided is quite compatible with the belief that biochemical investigation may one day make an important contribution to our understanding of schizophrenia. It is a false antithesis which poses a social approach as an alternative to a technical approach; and indeed the terms themselves are misleading. What is wanted is recognition that prevention and treatment of illness need a complex pattern of services, which range from social amenities to surgical procedures. The effective mobilisation of these services requires a revolution in thought and practice, which must be initiated and sustained from teaching centres.

The establishment of teaching hospitals, equipped and staffed so that they could make a contribution to the study of these problems, would be an event of tremendous significance in medical history. The path which medicine has followed hitherto, invaluable as it is, cannot alone provide the basis for mobilisation of the resources on which health is now known to depend. The organisation of teaching centres in such a way as to preserve the present tradition, but to add to it the wider concept of medical responsibility and interest, might rival in significance the sanitary revolution in the 19th century, and the impact of the Flexner report in the early 20th.

Conclusion

Irrespective of the way in which they are financed, the contemporary medical services are characterised by (*a*) separation of responsibility for the mentally ill, the chronic sick, and the acutely ill, and (*b*) a public-health service devoted exclusively to the prevention of disease. Responsibility is divided in this way because each class of patients presented to society at different times and as different problems; and the character of the public-health service is attributable to its development in a period when the outstanding challenge was infectious disease. Both features are unsuited to the main problems which medicine will face in future. These are: prenatal mortality; mental illness; and sickness and disability associated with ageing.

Improvement of the pattern of practice will require changes in medical education. At present the patients admitted to teaching hospitals are highly selected. This selection was traditional in voluntary hospitals and has been thought to be consistent with the requirements of scientific medicine. It has three serious disadvantages: it gives medical students a false impression of the medical task and of the methods appropriate to it; it prevents many of the ablest people from contributing to thought about the way in which medicine is to be practised; and, since it removes large segments of work from the vision of research-workers, and denies them access to representative populations, it has serious disadvantages in relation to medical research.

These disadvantages can be overcome by accepting responsibility from the teaching centre for all services, institutional and domiciliary, preventive and curative, for a defined area. This would create a laboratory within which it would be possible to explore new patterns of practice, to demonstrate to students the best arrangements consistent with contemporary knowledge and resources, and to promote important subjects and methods of medical research which have hitherto been neglected. It can be done without prejudice to traditional interests by making the size of the defined area such that numbers of representative patients derived from it are reasonable in relation to numbers of selected patients drawn from a much wider area for other research purposes.

At present we are attempting to prepare students for the practice of medicine by methods more appropriate to its advance. In the new teaching centre they would learn both to acquire new knowledge, and to make the best use of such knowledge as we already possess.

FURTHER EXPERIENCE WITH GUANETHIDINE

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THE ROYAL INFIRMARY, SHEFFIELD

HOWEVER promising a new hypotensive drug may appear initially, it is unlikely to be widely used today unless it is suitable for prolonged treatment, for administration of such a drug once started is likely to be required throughout life. Thus, although the efficacy of guanethidine is by now scarcely in doubt, any prospective user of the drug will need to be satisfied that side-effects are unlikely to cause undue hardship and, equally important, that drug tolerance will not eventually lead to loss of blood-pressure control. Since we have now had an opportunity to observe the behaviour of patients treated with guanethidine for twenty months and can provide some assurance on these points, it seemed appropriate to report briefly our further experience with this drug.

Material and Methods

Since the start of the trial at the Royal Infirmary, Sheffield, 114 patients have been treated with guanethidine—the majority of these for more than eleven months and none for less than six

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COMPLICATIONS DURING TREATMENT WITH GUANETHIDINE

Complication	Rate (%)
Orthostatic symptoms	52
Diarrhœa	44
Myalgia and muscle weakness	36
Exertional dyspnœa	17
Fluid retention	17
Nasal congestion	8
Frequency of micturition with or without stress incontinence	7
Sexual disorders	6
Dyspepsia	5
Shivering	3

months. During this time 6 patients died (3 from cerebrovascular accidents, 2 from uræmia, and 1 from a dissecting aortic aneurysm) and 8 abandoned treatment, usually on account of their objection to hypotensive symptoms. The remaining 100 patients are still receiving treatment, 44 of these having been managed exclusively in the outpatient department.

The scheme of dosage described in our earlier report (Leishman et al. 1959) has been maintained with only minor modification throughout this time, and we have continued our practice of observing the response to a single test dose before starting treatment with guanethidine. As far as possible additional hypotensive drugs were avoided, but in 11 cases hydrochlorothiazide was given to potentiate the effect of guanethidine and in a further 18 cases this drug was employed for its diuretic action.

Findings

CONTROL OF BLOOD-PRESSURE AND DOSE REQUIREMENTS

The blood-pressure is at present considered to be well controlled in 71 of the 100 patients who have been continuously treated with guanethidine. Thus, in 67 cases the standing diastolic pressure has fallen by 30 mm. Hg or more; and in the remaining 4 cases it is now consistently below 100 mm. Hg, although the reduction in diastolic pressure in these cases has been less than 30 mm. Hg. A further 18 patients have shown a moderate and probably adequate reduction of blood-pressure, but in 11 cases the response has been poor.

After the initial progressive increase necessary to achieve satisfactory blood-pressure control 71 patients have needed little or no change of dose, and although maintenance requirements have varied from as little as 10 mg. up to 150 mg., the majority are now taking between 20 mg. and 60 mg. daily. In 20 cases, on the other hand, it has been necessary to make one or more increases in dose in order to maintain blood-pressure control, while in the remaining 9 cases, whose blood-pressures are still uncontrolled, the dosage ultimately required is as yet unknown.

COMPLICATIONS (see table)

Hypotension

The frequent occurrence of hypotensive symptoms is in large measure a testimony to the drug's effectiveness. Although these symptoms were responsible for 8 patients discontinuing the drug, they were seldom a source of serious difficulty; and in contrast to experience with bretylium tosylate only 5 patients have described dizziness provoked by exertion. On the other hand, the exceptional capacity of guanethidine for reducing blood-pressure is not without hazard, for 6 patients have had transient attacks of weakness or paræsthesiæ which were clearly due to the unmasking by hypotension of latent cerebral arterial insufficiency.

Diarrhœa

Although this has been a common complaint it has usually been mild except when accompanying obvious drug overdosage. It is characteristically worse after food and in the mornings. We have found that in many cases it ceases spontaneously; but where treatment is needed, it responds readily to codeine phosphate 32 mg. taken once or twice daily before meals. Conventional measures of control such as kaolin or anticholinergic drugs have usually been less effective, and in our hands the response to pempidine tartrate also recommended for this complaint (Dollery et al. 1960) has been unreliable.

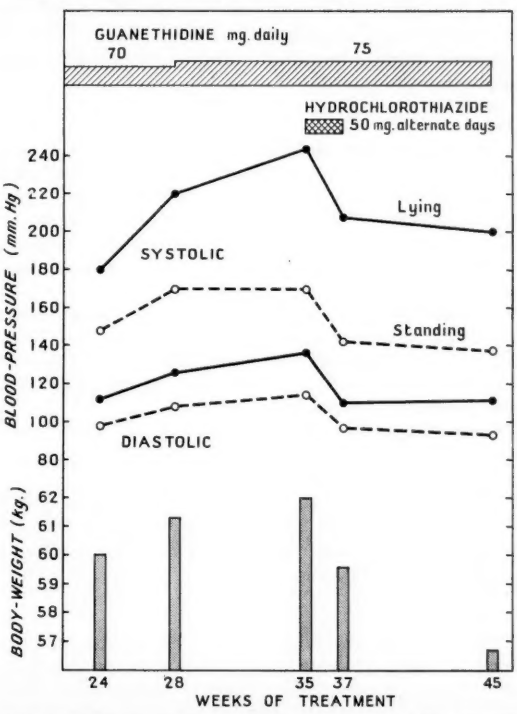
Myalgia and Muscle Weakness

Once we had learnt to avoid overdosing patients with guanethidine, symptoms of this type were never alarming; but there have been frequent complaints of muscle weakness and aching in the arms and legs, particularly during exercise. As with diarrhœa, these effects are often more prominent in the morning; they tend similarly to improve with time, and it has rarely been necessary to reduce the dose of guanethidine on this account. We have noted, however, that intermittent claudication is occasionally aggravated by treatment with guanethidine, and this must therefore be distinguished from the specific muscle effects of the drug.

Fluid Retention

Routine weighing of every patient receiving guanethidine has shown that many have gained weight (2 kg. or more) while on treatment. In 17 cases, however, the gain in weight was accompanied by increasing breathlessness which in a few cases was associated with raised jugular venous pressure and peripheral œdema. We observed also that in 13 of these patients the blood-pressure, which previously had been controlled and appeared stable, rose at this stage thus simulating the onset of drug tolerance.

Although in their advanced form these effects were indistinguishable from those of heart-failure, it seemed unlikely that their cause was primarily cardiac; but since



Fluid retention associated with temporary loss of blood-pressure control relieved by an oral diuretic.

the clinical picture was that of fluid retention diuretics were given temporarily and resulted in all cases in prompt diuresis, reduction in weight, and return of the blood-pressure towards its previously controlled level without change in the dose of guanethidine (see figure). Usually the signs of fluid retention did not recur when the diuretic was withdrawn.

These particular cases have not appeard to differ in any obvious respect from the remainder of the group; and it has not been possible to correlate the development of fluid retention with the dose of guanethidine, the severity of the hypertensive state (before treatment), or the appearance of any consistent pattern of renal defect. None of the patients in whom this syndrome developed showed signs of heart-failure when treatment with guanethidine was started, although 3 patients had had attacks of left ventricular failure during the preceding year and 4 gave a history of œdema in the past. Serum-electrolyte levels remained normal during phases of fluid retention, but in 8 cases this was associated with a moderate rise of blood-urea which persisted after diuretic drugs had been discontinued.

Comparable states of fluid retention have occasionally been recorded in patients treated with ganglion-blocking drugs, while an inverse relationship between sensitivity to hypotensive agents and blood-volume has also been demonstrated (Ronnov-Jessen 1960). It is possible therefore that the fluid retention with temporary loss of blood-pressure control observed in our patients was associated with an expanded blood-volume, but the mechanisms responsible for this remain at present obscure.

It is important from a practical point of view that the association of "pseudo-tolerance" and fluid retention should not be confused with true drug tolerance since the former responds readily to diuretics alone and is likely to be made worse if treated in error by increasing the dose of guanethidine. If patients receiving guanethidine are invariably weighed at each attendance this mistake should not commonly be made.

Other Complications

Other complications observed during treatment with guanethidine were in comparison unimportant. Breathlessness on exertion is a common symptom among hypertensive patients; but in 17 cases this appeared to be aggravated by treatment with guanethidine, although none of these patients showed any evidence of fluid retention.

The fact that the majority of our male patients were above middle age probably accounts for so few being aware of any disturbance of sexual function. Complaints of this nature referred usually to failure of ejaculation, and true impotence appeared to be rare.

Nasal congesion was occasionally a troublesome complication, although usually this could be relieved by an anti-histamine drug.

The patients who described shivering attacks had a normal urinary output of catechol-amines, and we have not encountered the persistent tremor noted by others as a side-effect of guanethidine.

TOLERANCE

When patients were continuously treated with ganglion-blocking drugs it was often found that progressively larger doses were needed to maintain the same reduction of blood-pressure. More recently, in the case of bretylium tosylate, this tendency of patients to develop drug tolerance proved a major obstacle to its long-term use, and we have naturally therefore been anxious to establish whether treatment with guanethidine will be similarly handicapped.

It is perhaps not surprising that the few reports so far available are conflicting (Dollery et al. 1960, Evanson and Sears 1960, Julian 1960, Page et al. 1961, Singh 1960) since observers will not necessarily agree in their definition of drug-tolerance. When reviewing our own cases we have, for this reason, adopted criteria which are deliberately strict, and have regarded an increase of 10 mg. in the daily requirement of guanethidine as indicating tolerance if previously the patient's blood-pressure had been well controlled on an unchanging dose.

By these standards 20 of the 100 patients under review have at some stage in their treatment developed true tolerance to guanethidine; but in most of these cases blood-pressure control was restored by a single small increase in daily dose, and only 3 patients have required frequent dose increments.

Tolerance was commonly first recognised between the fourth and seventh months of treatment but in 1 patient appeared after fourteen months of good control.

Discussion

While it has been satisfactory to find that the opinions we expressed earlier need little modification, the point of real importance which has emerged from this extended trial is that guanethidine is suitable for the long-term treatment of hypertension. Not only has its effectiveness been found to diminish very little with continued use but throughout the trial it has remained predictable in hypotensive effect and consistently easy to administer. For these reasons we regard guanethidine at present as the drug of choice for hypertension which previously would have been treated with ganglion-blocking drugs.

From the patient's point of view a hypotensive drug is scarcely ideal if, like guanethidine, it relieves hypertensive symptoms only to replace these by burdensome side-effects. However, with careful management, and especially the avoidance of large and rapid increases of dose, these side-effects can be minimised; and those of our patients who were previously treated with ganglion-blocking drugs have, without exception, expressed a preference for guanethidine.

The dose of a ganglion-blocking drug is commonly restricted by the advent of symptoms of parasympathetic blockade. Guanethidine is not subject to this restraint; and drastic reduction of blood-pressure, even to normotensive levels, is frequently possible with this drug. We cannot, however, agree with those who regard this as the sole objective of hypotensive drug treatment; for, apart from the considerable hazard to those with cerebrovascular insufficiency, a drastically reduced blood-pressure presents an intolerable burden to most patients. The favourable progress of hypertensive patients treated in earlier days either by lumbodorsal sympathectomy or by ganglion-blocking drugs has shown what can be achieved by modest and even intermittent reduction of blood-pressure (Leishman 1959), and it has yet to be established that hypotensive treatment on a more ambitious scale will necessarily improve on these results.

After twenty months' experience with guanethidine it seems now safe to conclude that tolerance is unlikely to be a serious problem with this drug. Our own observations have suggested that approximately 1 in every 5 patients treated with guanethidine is likely to develop some

degree of drug tolerance, but in most of these cases this will be easily overcome by increased dosage and it will be exceptional for tolerance to interfere seriously with treatment.

Summary

The results of twenty months' observation of hypertensive patients continuously treated with guanethidine are reported.

Of the original 114 patients who started treatment 6 have died and 8 have discontinued the drug.

Of the remaining 100 patients the blood-pressure is considered well controlled in 71 and moderately well controlled in 18. In 11 cases the response has been poor.

Complications have been common, and attention is especially drawn to the association of fluid retention and temporary loss of blood-pressure control. The need to distinguish this from true drug tolerance is emphasised.

True drug tolerance has occurred in 20% of our patients, but except in 3 cases this has been easily overcome by a small and usually single increase in dose. It has been exceptional for drug tolerance to interfere seriously with treatment.

Guanethidine is an effective hypotensive drug which is suitable for long-term treatment of patients with moderate or severe hypertension. If treatment is conducted with care, side-effects of the drug, although common, can be reduced to an acceptable level.

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ERYTHROMYCIN-RESISTANT STAPHYLOCOCCUS AUREUS

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IT is now generally accepted that prolonged and unrestricted clinical use of an antibiotic is associated with an increased incidence of resistant bacterial strains. This phenomenon has been observed most distinctly in relation to strains of *Staphylococcus aureus* encountered in hospital.

Erythromycin was introduced for clinical use in 1952 (McGuire et al. 1952). The work of Lepper et al. (1953) indicated that erythromycin-resistant staphylococci could be expected at least as commonly as those resistant to antibiotics already in use, and Hobson (1954) demonstrated how, in vitro, high degrees of resistance could be readily acquired. In view of these findings, it was hoped that erythromycin would be dispensed with discretion, and so limit the emergence and spread of resistant bacterial strains (Forfar and Maccabe 1957). Although erythromycin-resistant strains have been reported from time to time, their proportion has been relatively low compared with that of strains resistant to other antibiotics in common use. In Edinburgh until 1955 we had encountered only one small outbreak of infection due to an erythromycin-resistant staphylococcus. Nevertheless, we did suggest at that time that there was considerable danger that such a strain might, under favourable conditions, spread within the community (Maccabe and Gould 1956).

The recent introduction of other antibiotics active against antibiotic-resistant staphylococci may have resulted in a more liberal use of erythromycin in the treatment of staphylococcal infections. This increased usage of erythromycin would be expected to encourage the appearance of such strains and their subsequent spread, and reports show that the proportion of erythromycin-resistant staphylococci is increasing in some hospitals (Bauer et al. 1960).

We describe here an investigation carried out between July, 1958, and August, 1960, into the appearance of an erythromycin-resistant staphylococcus in a 400-bed general hospital with a busy outpatient department, and the maintenance and spread of this strain throughout the hospital. Methods to reverse or limit this trend are suggested.

Materials and Methods

Swabs from lesions and other sites were inoculated on to plates of blood-agar and milk-agar media (Cruickshank 1960). Representative colonies were subcultured in nutrient broth. These broth cultures were tested for coagulase production by the method of Fisk (1940), and susceptibility to a set of staphylococcal phages (at routine test dilution and undiluted) by the method of Williams and Rippon (1952). Sensitivity tests to penicillin, streptomycin, tetracycline, chloramphenicol, sulphonamide, and erythromycin were performed by the disc technique of Gould and Bowie (1952). Discs containing 10 μg. of erythromycin were used, a zone of inhibition of 15 mm. diameter corresponding to an inhibitory concentration of 2 μg. per ml. Strains were considered resistant to erythromycin if they required more than 2 μg. per ml. for inhibition.

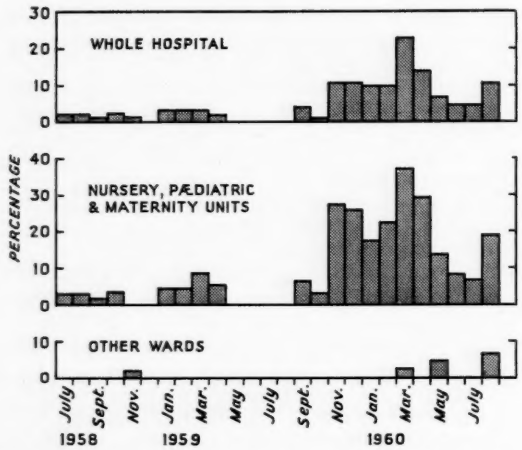
Airborne dust was sampled with a slit sampler delivering 1 c.ft. of air per minute on to a blood-agar plate (total bacterial count) and salt-milk agar (*Staph. aureus* count). The surfaces of fomites were sampled by rubbing with a swab or applying a strip of adhesive tape which were transferred to the surface of milk-agar plates.

Findings

During this survey, 2521 strains of *Staph. aureus* from lesions were examined (table I). Of these, 1681 were isolated between July, 1958, and October, 1959, and 28 (1·7%) were resistant to 2 μg. per ml. or more of erythromycin. 840 lesion strains were isolated between

TABLE I—NUMBER OF ERYTHROMYCIN-RESISTANT *Staph. aureus* STRAINS ISOLATED FROM LESIONS EXAMINED IN THE HOSPITAL FROM JULY, 1958, TO AUGUST, 1960

Month	No. of strains		Month	No. of strains	
	Total	Erythromycin-resistant		Total	Erythromycin-resistant
1958:			Aug. ..	69	0
July ..	135	3	Sept. ..	69	3
Aug. ..	113	3	Oct. ..	102	1
Sept. ..	132	1	Nov. ..	105	12
Oct. ..	122	3	Dec. ..	72	8
Nov. ..	102	1	*1960:*		
Dec. ..	110	0	Jan. ..	70	7
1959:			Feb. ..	80	8
Jan. ..	114	3	March ..	96	22
Feb. ..	113	4	April ..	108	15
March ..	113	4	May ..	72	5
April ..	104	2	June ..	81	4
May ..	102	0	July ..	67	4
June ..	94	0	Aug. ..	89	10
July ..	87	0	Total	2521	123


WHOLE HOSPITAL
NURSERY, PÆDIATRIC & MATERNITY UNITS
OTHER WARDS
PERCENTAGE
July Sept. Nov. Jan. Mar. May July Sept. Nov. Jan. Mar. May July
1958 1959 1960

Erythromycin-resistant strains isolated each month from lesions (percentage of all strains isolated).

November, 1959, and August, 1960, and 95 (11·3%) were erythromycin-resistant. The majority were resistant to 10 μg. or more per ml. of erythromycin.

The accompanying figure shows the percentage of strains of *Staph. aureus* isolated from infected lesions in the hospital, which were resistant to erythromycin, during the period July, 1958, to August, 1960.

It will be seen that the resistance-rate was low from July to November, 1958, after which it fell to zero. The rate increased slightly from January to April, 1959, and once again returned to zero before a very considerable rise in November, 1959, which was maintained until August, 1960. The greatest number of erythromycin-resistant strains were isolated in the newborn nursery and pædiatric and maternity units, and their appearance in these units preceded that in other units in the hospital. Only an occasional erythromycin-resistant strain of *Staph. aureus* had been isolated from other geographically more distant units in the hospital. Both strains isolated from out-patients were from breast abscesses which may have been contracted when the patients were in the maternity unit.

TABLE II—RESULTS OF BACTERIOPHAGE-TYPING OF 2521 STRAINS OF *Staph. aureus* ISOLATED FROM LESIONS

Percentage with phage pattern of group:				Percentage with antibiogram:						
I	II	III	N.T.	P.S. S.S. C.S. O.S. E.S.	P.R. S.S. C.S. O.S. E.S.	P.R. S.R. C.S. O.S. E.S.	P.R. S.R. C.S. O.R. E.S.	P.R. S.R. C.S. O.R. E.R.	P.R. S.R. C.R. O.R. E.R.	Others
27	5	56	12	21	19	34	16	3	2	5

N.T. = not typable. P = penicillin. S = streptomycin. C = chloramphenicol. O = oxytetracycline. E = erythromycin. S = sensitive. R = resistant.

The majority of erythromycin-resistant strains of *Staph. aureus* isolated from lesions (tables II and III) in all three episodes had the same phage pattern (type 75/76/77) which belongs to group III. This erythromycin-resistant strain is similar in pattern to that isolated previously in this and other hospitals in Edinburgh (Maccabe and Gould 1956).

Table III shows the phage pattern of 122 erythromycin-resistant strains isolated during this survey. All but 10 were of pattern 75/76/77; 1 was of type 47, 4 were of type 52/52A/79/80, 1 was of type 42B/52A/73, and 4 were untypable. The majority of these other strains were isolated from lesions in the nursery.

Tables IV and V record the percentage of erythromycin-resistant strains isolated from carriers, fomites, and airborne dust in the nursery and other sites in the hospital. Before the outbreak of erythromycin resistance starting in November, 1959, no erythromycin-resistant strain was isolated. More recently, however, large numbers of such strains have been isolated from the environment, from the anterior nares of nurses and patients in the nursery and medical and surgical pædiatric departments. Colonies of erythromycin-resistant staphylococci were isolated in appreciable numbers from tables, taps, tap-handles, window-ledges, and weighing-scales in the nursery and pædiatric wards.

Discussion

Acquired bacterial resistance to antibiotics and hospital cross-infection are so intimately connected that they must be considered together.

It is believed that antibiotic-resistant bacteria arise by selection of spontaneously occurring resistant mutants which may be present in any bacterial population. The selection of these resistant mutants depends on selective factors present in the environment, which may be in the patient's tissues or in sites outside the patient which harbour the organism. In both, the antibiotic will act as an important selective factor by eliminating the sensitive cells, but not those resistant (Gould 1958). The latter may survive, multiply, and establish themselves. It is therefore clear that the more an antibiotic is used, the greater is the likelihood of resistant strains emerging.

TABLE III—PHAGE PATTERNS OF 122 ERYTHROMYCIN-RESISTANT STRAINS OF *Staph. aureus* ISOLATED FROM LESIONS IN THE HOSPITAL

Source	No. of strains	Phage pattern (R.T.D.)				
		75/76/77	47	52/52A/79/80	42B/52A/73	N.T.
Nursery	58	51	..	3	1	3
Surgical pædiatric	29	29	..	..	..	..
Medical pædiatric	16	16	..	..	..	..
Other sites ..	19	16	1	1	..	1

N.T. = not typable.

Not all strains of bacteria of any given species produce spontaneous mutants which are naturally resistant to antibiotics; thus penicillin-resistant mutants of *Streptococcus pyogenes* do not appear to exist, and the penicillin susceptibility of strains of this species remains uniform. Apparently only a limited number of strains of *Staph. aureus* have mutants which are naturally resistant to antibiotics. Therefore, of the many different strains of this organism found in communities not exposed to the antibiotics, only a small proportion are resistant, and only some of these occur as antibiotic-resistant strains in closed communities—e.g., hospitals—where antibiotics are used. In consequence, the number of different types of resistant strains isolated in hospital is limited (Forfar et al. 1955). The appearance of erythromycin-resistant strains of *Staph. aureus*

TABLE IV—RECOVERY OF *Staph. aureus* FROM AIRBORNE DUST IN THE HOSPITAL ENVIRONMENT

Site and time	Total bacterial count (per 100 c.ft.)	*Staph. aureus* (%) in total count	Strains of *Staph. aureus* erythromycin-resistant (%)
Nursery:			
Sept., 1959	1400	2·8	0
Oct., 1960	1560	2·5	8
Medical pædiatric ward:			
Sept., 1959	1800	1·7	0
Oct., 1960	2000	3·0	2
Surgical pædiatric ward:			
Sept., 1959	2400	2·2	0
Oct., 1960	2300	4·5	10
General surgical ward:			
Sept., 1959	1000	1·0	0
Oct., 1960	2600	0·8	1
Gynæcological ward:			
Sept., 1959	1920	2·0	0
Oct., 1960	2800	2·4	1

Each figure is an average of four observations.

TABLE V—RECOVERY OF *Staph. aureus* FROM ANTERIOR NARES OF STAFF AND PATIENTS, AND ALSO FROM FOMITES

Site	Time and source	No. examined	Carriers (%)	Carrier strains erythromycin-resistant (%)
Nursery	*Sept., 1959:*			
	Babies ..	100	58	0
	Mothers ..	89	19	0
	Nurses ..	20	65	0
	Oct., 1960:			
	Babies ..	36	40	60
	Mothers ..	30	27	0
	Nurses ..	40	45	11
Pædiatric dept.	*Sept., 1959:*			
	Patients ..	..	..	..
	Nurses ..	14	70	0
	Oct., 1960:			
	Patients ..	26	60	50
	Nurses ..	32	55	6

Fomites (table-tops, tap-handles, window-ledges, weighing-scales): Sept., 1959, *Staph. aureus* frequently isolated and all strains erythromycin-sensitive; Oct., 1960, *Staph. aureus* frequently isolated and many strains erythromycin-resistant.

will therefore depend primarily on the presence of a strain of the organism which produces spontaneous mutants naturally resistant to this antibiotic. This may occur quickly and would explain the results of Lepper et al. (1953), who found that the hospital staphylococcal population, which was sensitive to erythromycin, was almost completely replaced within five months by erythromycin-resistant staphylococci.

Until the episode in 1958, we had not experienced a high erythromycin-resistance rate despite the fact that considerable amounts of erythromycin had been used in one unit of this hospital for five years. This may well have been due to the good fortune that no strain producing resistant mutants had been introduced and been able to establish itself. One such strain was encountered about mid-1958, in the nursery, where erythromycin is used to the greatest extent. Initially the establishment of this strain was in doubt, although a small number of cases of infection due to it occurred in the nursery and adjacent ward. A second outbreak of infection due to erythromycin-resistant staphylococci of the same phage-type occurred a few months later. On this occasion the incidence of infection was greater; the infections extended over a longer period than in the first episode, and the spread of this strain could be traced to adjacent units. Once more, this particular strain did not appear to establish itself, and for some months after April, 1959, no erythromycin-resistant staphylococci were isolated until a sudden and pronounced increase in the number of infections due to such strains occurred towards the latter part of 1959. This third episode has proved to be much more long-lasting, and the dissemination to other units much more extensive. The great majority of erythromycin-resistant strains isolated were of the same phage-type and identical with those isolated in the two previous episodes.

It seems reasonable to conclude that this particular strain of *Staph. aureus*, capable of existing in the erythromycin-resistant form, has become endemic in this hospital environment, and has been encouraged to establish itself and spread by various environmental factors, one of the most important of which undoubtedly is erythromycin. The potential dangers of such strains are obvious, especially as occasionally they have been found resistant to all the commonly used antibiotics. Such strains are disseminated by cross-infection; and the more numerous the sources of growth of these strains, the greater will be the dissemination. During dissemination these strains will encounter new hosts which will tend to increase their virulence.

The aim must be to discourage further emergence, establishment, and spread of such strains, and, if possible, to eradicate them from the hospital environment. An important measure is the complete withdrawal of erythromycin for a period, or its administration only to seriously ill patients where clinical and bacteriological findings require its use. Every hospital should adopt a strict policy for the use of antibiotics which should be periodically reviewed in the light of their antibiotic-resistance rates (Barber et al. 1960). Carriers and fomites should be screened bacteriologically and steps taken to prevent resistant strains, when detected, from contaminating the environment. In addition, measures to control cross-infection should be constantly applied (Ministry of Health 1959).

Summary

91% of erythromycin-resistant strains of *Staphylococcus aureus* isolated in a 400-bed hospital over a two-year period were of the same phage-type (group III pattern). This strain, first isolated sporadically from infections in the maternity and pædiatric departments, eventually established itself in these units and spread to other units of the hospital, and was recovered from nasal carriers, airborne dust, and fomites.

It is suggested that there are a limited number of strains of *Staph. aureus* capable of existing in an erythromycin-resistant form, and it is a matter of chance whither these are introduced into the hospital environment. Establishment and spread of such strains is encouraged by the use of the antibiotics. Limitation in the use of erythromycin, bacteriological examinations to detect the presence of resistant strains, and means to prevent cross-infection will reduce the chance of establishment and spread of such strains.

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" . . . It is frequently said that doctors and other professional people are lucky, since their work is interesting and creative, and for them it is hard to define exactly where work begins and ends: it is deduced from this that although the professional person indeed puts in long hours they are without ill effect on his health and that the contrary is true of people in other walks of life because the work they do lacks interest and is not creative. It may be true to say that a workman is able to draw a sharper distinction between work and recreation than the professional man but it seems to me unwarrantable and arrogant to assume that what appears dull and uninteresting to an outside observer necessarily seems so to those who undertake jobs of this sort. I said earlier that work dominates the lives of most people, and is indeed their major interest. Anyone who will encourage workmen to talk about themselves will soon prove the truth of this, and may also be surprised to hear of the satisfaction which they gain even from so-called unskilled jobs which often require more skill than is supposed. So all in all I really cannot accept the thesis that relatively long hours of work of themselves are necessarily detrimental to health."—Dr. G. F. KEATINGE in the Wyers memorial lecture, 1960 (*Trans. Ass. industr. med. Offrs*).

PYRIDOXINE-RESPONSIVE HYPOCHROMIC ANÆMIA

A Report of Two Cases

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IN recent years a number of cases of hypochromic anæmia, unresponsive to iron, have proved treatable by other means. Several reports have described the successful use of pyridoxine.

In animals, experimental dietary deficiency of pyridoxine has produced hypochromic anæmia (Fouts et al. 1940, Wintrobe et al. 1943, Kornberg et al. 1945). The first report in man of anæmia which responded to pyridoxine was by Smith and Martin in 1940; when studying the effect of the vitamin on cheilosis, they found an anæmia in a 7-year-old girl with nutritional deficiency which improved with pyridoxine alone. Unfortunately, no hæmatological data were given. Snyderman et al. (1950) described anæmia, induced artificially by a pyridoxine-deficient diet in a microcephalic infant, which responded to pyridoxine.

The first naturally occurring and fully documented case was that of Harris et al. (1956), and another in this country was reported recently by Jones and Hutt (1961). The salient points of recorded cases are shown in the table. The patients usually present with anæmia which shows a peripheral blood-picture identical with that of iron deficiency yet does not repond to iron therapy by mouth or injection. Further investigation reveals that, in fact, iron deficiency is not present, as shown by normal or high serum-iron levels and much excess stainable iron in the bone-marrow. The diagnosis is confirmed by the dramatic response to pyridoxine treatment.

We here describe two further cases: the first one has been briefly reported elsewhere (Leeming and Wilkinson 1959).

Case-reports

THE FIRST CASE

A vehicle mechanic, aged 40, was admitted to the Manchester Royal Infirmary on July 11, 1957. He gave a 17-year history of periodic mild dyspepsia. In the previous April he had had a small hæmatemesis, shortly after which his hæmoglobin (Hb) was 11·8 g. per 100 ml. A barium-meal showed a duodenal ulcer and a diverticulum at the junction of the first and second parts of the duodenum. After temporary improvement admission to hospital became necessary because of increasing pallor and weakness. His diet had been adequate and he had taken no drugs except antacids. There was no history of consanguinity. Seven members of his family were later examined. Blood-counts and serum-iron levels were normal except for his mother, who had an iron-deficiency anæmia.

DATA OF RECORDED CASES WITH PYRIDOXINE-RESPONSIVE ANÆMIA

Authors	Sex	Age (yr.)	Diet	Serum-iron (µg. per 100 ml.) before and after pyridoxine	Hb levels (g. per 100 ml.) M.C.H.C. (%)		Tryptophan metabolism
					Initial	Final	
Snyderman et al. (1950, 1952)	M	8/12	Pyridoxine-deficient (artificial)	Not done	5·5 g. 34% (red cells hypochromic)	Hb approaching normal	Inability to convert tryptophan to N-methyl nicotinamide
Harris et al. (1956, 1958)	M	27	3 mg. per day of pyridoxine (adequate to authors)	Before: 170 (92% saturation) After: 214 (31% saturation)	4·5 g. (red cells hypochromic)	14·1 g. 27·2%	Loading tests gave abnormal excretion of breakdown products; normal after treatment
Maier (1957)	F	67	Not stated	Before: 160	9·0 g.	10·4 g.	Normal, but only tested after treatment
Foy and Kondi (1958)	M	35	Normal	Not done	8·3 g. 24%	11·0 g. 28·2% (after 14 days)	No tests done
Gehrmann (1958)	M	43	,,	Before: 230 After: 137	7·8 g.	Normal	Xanthurenic-acid excretion increased after tryptophan; not repeated after treatment
Bishop and Bethell (1959)	M	13	,,	Before: 162 After: 127	7·0 g. 25·9%	9·6 g. 24·0%	Normal before and after treatment
Erslev et al. (1960)	M	52	Normal (with possible excess alcohol)	Before: 278 (85% saturation)	3·8 g. 22·0%	12·8 g. 26·0%	High excretion of xanthurenic acid after tryptophan load, with reversion to normal after treatment
Verloop and Rademaker (1960)	M	37	Deficient in pyridoxine from 1942 to 1945 (about 0·5 mg. per day); thereafter normal	Before: 365 (100% saturation) Remained high after treatment	8·4 g. 23%	10·1 g. (red cells still hypochromic)	Normal xanthurenic acid excretion before and after treatment, with and without tryptophan load
Jones and Hutt (1961)	M	49	Normal	Before: 345 After: 318	8·7 g. 28%	13·3 g. 30%	Loading tests normal
Present case 1	M	40	,,	Before: 162 After: 78 (40% saturation)	5·9 g. 25·0%	15·3 g. 27·5%	No tests done
Present case 2	M	46	,,	Before: 205 (85% saturation) After: 79 (40% saturation)	5·2 g. 27·5%	13·8 g. 30·0%	,, ,, ,,

Investigations and Progress

The skin and mucous membranes were very pale, and he had epigastric tenderness, but no other abnormal signs. The Hb was 5·9 g. per 100 ml., red cells 3·06 million per c.mm., colour-index (C.I.) 0·6, packed-cell volume (P.V.C.) 23·5%, mean corpuscular Hb concentration (M.C.H.C.) 25%, mean corpuscular volume (M.C.V.) 77 c.μ, and white cells 4800 per c.mm., with a normal differential count. Platelets were normal in the film. The red cells showed extreme anisocytosis and poikilocytosis, with marked hypochromia and anisochromia. Occasional target cells were seen (fig. 1). The sternal marrow showed intense erythroid hyperplasia, with numerous mitotic figures. Maturation was normoblastic but unusually large early forms were fairly numerous, with nuclei staining less deeply than usual and with a nuclear pattern which was not typical of normal pro-erythroblasts. The other cells series were normal. Several occult-blood tests on the stools were weakly positive. Serum-bilirubin was 0·5 mg. per 100 ml., alkaline phosphatase 5·5 King-Armstrong units per 100 ml., thymol-turbidity 0·6 units, serum-albumin 4·0 g. per 100 ml., and serum-globulin 2·0 g. per 100 ml. Blood urea was 38 mg. per 100 ml. A fractional test-meal showed a high normal secretion of free acid.

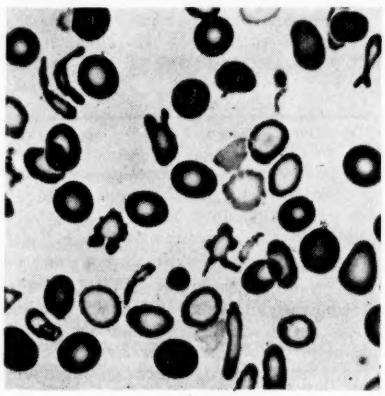

Fig. 1—The first case: blood film (×690).

Transfusion of 2 pints of concentrated red cells raised his Hb to 8·3 g. per 100 ml., but in 3 weeks it had fallen to the previous level. The effect of a further blood-transfusion was equally transient. A bleeding duodenal ulcer seemed the most likely diagnosis, and Mr. R. L. Holt was consulted; but he did not advise surgery. Intravenous iron (710 mg. of elemental iron) had no effect. The serum-iron level (Ramsay 1953) before this therapy was 200 μg. per 100 ml.

A direct Coombs test was negative, and the osmotic fragility of the red cells was slightly decreased. An oral glucose-tolerance test, and the fæcal fat content, were normal. A marrow aspirate showed an increased hæmosiderin content, and many of the early normoblasts had hæmosiderin granules in their cytoplasm. Folic acid was given by mouth in a dose of 10 mg. b.d. The reticulocyte-count reached 7% on the 10th day (fig. 2), when the patient was discharged at his own request. After 26 days the Hb had risen to 8·1 g. per 100 ml. Folic acid intramuscularly had no further effect, and from October he was also given vitamin B_{12} intramuscularly 1000 μg. weekly. His Hb rose slowly, reaching 11·8 g. per 100 ml. $2^1/_2$ months later, when his red-cell count was 5·5 million per c.mm., and the M.C.H.C. had fallen to 22%. The survival of his own red cells was normal (^{51}Cr). The intestinal absorption of radioactive vitamin B_{12} was normal. His hæmoglobin was electrophoretically normal, and concentration of fœtal hæmoglobin (1·25%) was normal.

During this time the patient complained of various abdominal pains for which no cause was found. The spleen was now palpable. Despite continued therapy with folic acid and vitamin B_{12} the Hb fell again, and additional treatment with ascorbic acid, proteolysed liver, prednisone, and cobalt chloride had no effect. Tetracycline (250 mg. q.i.d.) was given for 7 weeks, with only a transient effect on the Hb. Because several serum-iron estimations were either normal or increased (114–260 μg. per 100 ml.) and a repeat sternal marrow, in April, 1958, again showed excess hæmosiderin, no iron therapy was given.

Treatment with Pyridoxine

At the beginning of July his Hb was 6·2 g. per 100 ml., M.C.H.C. 22·2%, and reticulocytes less than 1%. Pyridoxine hydrochloride was started by mouth in a dose of 120 mg. daily (not 60 mg. daily as reported previously). 7 days later the reticulocytes had risen to 7%, and the Hb was 11·0 g. per 100 ml. (fig. 2). After 4 weeks the Hb was 13·2 g. per 100 ml., and the serum-iron 78 μg. per 100 ml. (saturation 40%). By September the Hb had reached 16·3 g. per 100 ml., and the red cells 6·89 million per c.mm., and the dose of pyridoxine was reduced to 80 mg. daily. The patient failed to keep his next appointment, and he discontinued therapy after 4 months. In May, 1959, his Hb had fallen to 9·6 g. per 100 ml. Then, and again in October, short courses of pyridoxine (in daily doses of 40 mg. and 20 mg. respectively) were given with rapid improvement (fig. 2). Since March, 1960, pyridoxine hydrochloride has been given continuously (40 mg. daily, reducing to 20 mg. daily). On Nov. 10 the Hb was 15·3 g. per 100 ml., M.C.H.C. 27·5%, and serum-iron 115 μg. per 100 ml. No other therapy has been given since September, 1958.

THE SECOND CASE

A Post Office engineer, aged 46, was admitted to Crumpsall Hospital on Oct. 14, 1959, with 2 weeks' history of palpitation and increasing dyspnœa. He had had mild dyspepsia for 5–6 years, with burning epigastric pain radiating to the front of the chest, worse about an hour after food, and relieved by alkalis; it became worse on bending down, and he had noticed it

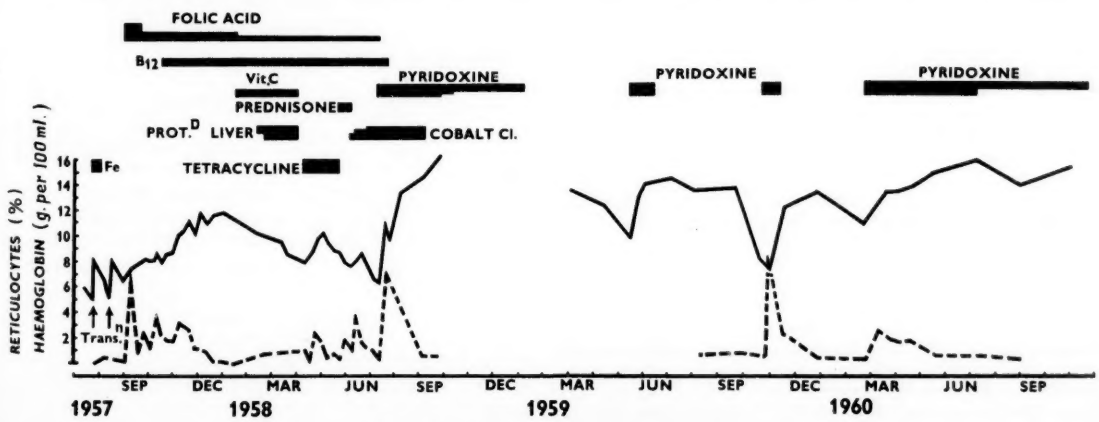

Fig. 2—The first case: course and treatment.

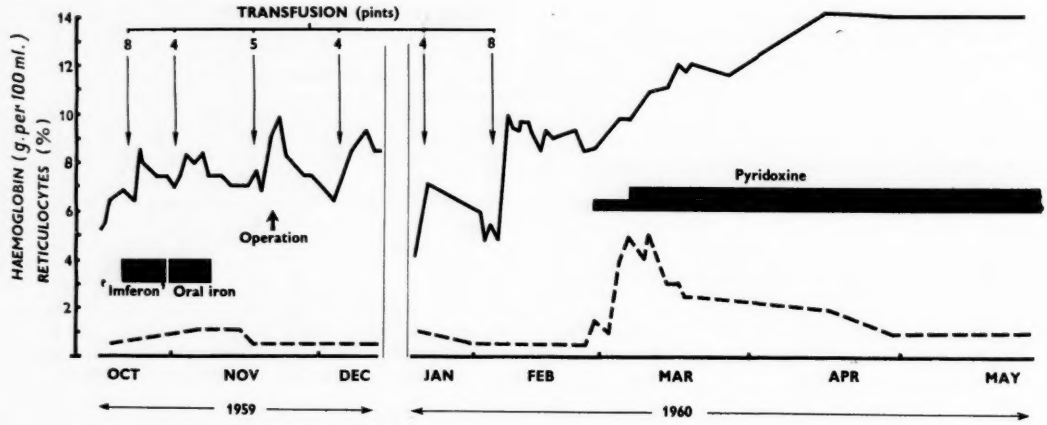

Fig. 3—The second case: course and treatment.

sometimes in bed. His diet had been normal. When he was seen at the hospital in 1951, with brachial neuritis, his Hb was 14·0 g. per 100 ml. There was a history of consanguinity, the patient's father having married the daughter of a first cousin.

Investigations and Progress

He had extreme pallor of the skin and mucous membranes, but no other abnormal physical signs. The Hb was 5·2 g. per 100 ml., red cells 2·28 million per c.mm., C.I. 0·8, P.C.V. 19%, M.C.V. 82 c.μ, M.C.H.C. 27·5%, and white cells 9600 per c.mm., with a normal differential count. The platelets were normal in the film. The direct Coombs test was negative, and osmotic fragility of the red cells was not increased. The serum-bilirubin was 1·0 mg. per 100 ml., alkaline phosphatase 5 K.-A. units per 100 ml., thymol-turbidity 1·0 unit, thymol-flocculation 0, and colloidal gold 0. The blood-urea was 33 mg. per 100 ml. The urine contained 0·3 mg. of urobilinogen per 24 hours. Occult-blood tests on the stools were positive seven times and negative twice. A barium-meal showed much regurgitation into the œsophagus, and some narrowing in the pyloric region.

Repeated blood-transfusions (12 pints) did not produce a sustained rise in Hb, and no effect resulted from iron intramuscularly (2500 mg. of elemental iron) followed by ferrous gluconate by mouth (fig. 3). A sternal marrow smear was hypercellular, with normoblastic erythropoiesis and defective hæmoglobinisation. Iron stores were increased. The picture seemed to be that of an iron-deficiency anæmia under treatment.

A bleeding œsophageal hiatus hernia was suspected, and accordingly Mr. H. A. Haxton was consulted. He performed a laparotomy on Nov. 19, after a further blood-transfusion of 5 pints. There was no hernia but the œsophageal hiatus, which was obviously lax, was tightened. The pyloric region of the stomach was thickened though not ulcerated, but in view of the symptoms a Billroth-I gastrectomy and a vagotomy were performed. The patient has had no further dyspepsia. Before discharge from hospital, on Dec. 17, another blood-transfusion was required. As an outpatient he was given iron by mouth.

On Jan. 20, 1960, he was seen again because of increasing anæmia. Except for small flame-shaped hæmorrhages in both fundi, there were no new signs. The blood-picture was: Hb 4·0 g. per 100 ml., M.C.V. 75 c.μ, M.C.H.C. 25%, and reticulocytes 1·0%. The film showed hypochromia, some anisocytosis, and striking poikilocytosis. No target cells were seen. The patient was admitted to hospital and given further blood-transfusions. The transfused red cells showed normal survival (^{51}Cr), and liver-function tests were normal. A test-meal showed the presence of free acid. On a normal diet average fæcal fat excretion was 6 g. per day (4-day estimation). A glucose-tolerance test was normal. The serum-iron (Ramsay 1957a) was 205 μg. per 100 ml., and the total serum-iron-binding capacity (Ramsay 1957b) was 240 μg. per 100 ml., giving 85% saturation (normal saturation 30–45%). On electrophoresis Hb was normal, and its alkali-resistant fraction was less than 2%. Another sternal marrow film was hypercellular, with the myeloid/erythroid ratio 1/4. Erythropoiesis was normoblastic, with very defective hæmoglobinisation. The majority of erythroid precursors were intermediate forms, many with scanty cytoplasm. The prussian-blue reaction showed a gross excess of stainable iron and many normoblasts with siderotic granules in their cytoplasm (sideroblasts).

Treatment with Pyridoxine

Pyridoxine hydrochloride was started by mouth on Feb. 26, 1960, in a dose of 20 mg. daily for 7 days, then it was increased to 100 mg. per day. Immediately the patient felt better, and there followed a reticulocyte response and rise in Hb level (fig. 3). The serum-iron 10 days after the start of treatment was 79 μg. per 100 ml. (saturation 40%). A further sternal marrow film showed a myeloid/erythroid ratio of 1·9/1. Erythropoiesis was normoblastic, and maturation was more normal. The cytoplasm of the later forms was more abundant but hæmoglobinisation was still defective. Iron stores were greatly increased, and sideroblasts were again demonstrable.

The patient was discharged on March 22. On April 17 his Hb was 14·2 g. per 100 ml., red cells 5·05 million per c.mm., C.I. 1·0, P.C.V. 47%, M.C.V. 94 c.μ, M.C.H.C. 30·5%, and reticulocytes 2%. Since then he has continued to take pyridoxine 100 mg. daily. He has remained extremely well, and the blood level has been maintained. His most recent serum-iron (Nov. 5) was 78 μg. per 100 ml., with a saturation of 33%. The M.C.H.C., however, has not risen above 30·5%.

Discussion

Both our patients were men, aged 40 and 46, who presented with a hypochromic anæmia, at first thought to be due to upper gastrointestinal bleeding. The evidence for this seemed so convincing that operation was considered in both cases, and actually performed in the second.

Despite all attempts at therapy with iron and blood-transfusions the hæmoglobin could not be maintained at a satisfactory level. Investigations excluded iron deficiency, aplasia, and hæmolysis. The high serum-iron levels and increased deposits of hæmosiderin in the marrow, in the presence of hypochromia, suggested failure of iron utilisation.

The differential diagnosis of this hæmatological picture includes several conditions of which thalassæmia is the best known.

In our patients the absence of Mediterranean ancestry and

a family history of anæmia, and the appearance of anæmia in adult life, made this diagnosis unlikely. It was finally excluded by finding normal hæmoglobin on electrophoresis, and no increased fœtal hæmoglobin. Moreover, the first case showed very few target cells in the blood, and the second case had none. Rarer hæmoglobinopathies were also excluded by the normal hæmoglobin electrophoresis and the absence of family history. The refractory normoblastic anæmia of Dacie et al. (1959) is usually macrocytic, and hypochromic cells are infrequent. Di Guglielmo's disease had to be considered because of the striking erythroid activity in the bone-marrow, with an increase in early forms, some showing megaloblastic features. But against this diagnosis were the absence of multinucleated erythroblasts and the paucity of myeloblasts in the bone-marrow, and the lack of nucleated red cells in the peripheral blood.

There is a group of diseases, possibly of common ætiology (Dacie 1960), which can only be satisfactorily differentiated by their failure to respond to pyridoxine. These include hypochromic iron-loading anæmia (Crosby and Sheehy 1960), hereditary hypochromic sideroachrestic anæmia (Heilmeyer et al 1958), familial hypochromic anæmia (Mills and Lucia 1949), and refractory hypochromic anæmia (Garby et al. 1957). Rundles and Falls (1946) described a refractory hypochromic anæmia in two families, in which many members of several generations were affected. One of their cases has recently been shown to respond to pyridoxine (Bishop and Bethell 1959). As well as these cases, a patient with pellagra and severe hypochromic anæmia responding to nicotinic acid but not to iron, has been reported by Foy and Kondi (1958). Horrigan et al. (1957) had two male patients, aged 38 and 41, who only responded to a crude liver extract which did not contain pyridoxine. The hæmatological features in these two patients were identical with those found in pyridoxine-responsive anæmia. This illustrates the crucial importance of the therapeutic trial.

In clinical practice the most common causes of a disturbance in iron utilisation are neoplasms, chronic infections, and rheumatoid arthritis. These conditions, however, rarely produce such severe hypochromia as our patients had. Chronic lead poisoning has to be considered but should not present diagnostic difficulty.

The mechanism of production of pyridoxine-responsive anæmia has not been satisfactorily elucidated. Theoretically a true deficiency of pyridoxine could be due to defective diet, malabsorption, or impaired bacterial synthesis in the bowel. On the other hand, a conditioned deficiency may result from interference with pyridoxine metabolism. Apart from the patient of Smith and Martin (1940), there is no convincing evidence that dietary deficiency has played a part in the naturally occurring cases, nor was this a factor in our patients. This type of anæmia does not seem to be related to the malabsorption syndrome. Whether pyridoxine synthesis by bacterial action in the bowel is important in man has not been established (Vilter 1955). It seems, therefore, that there is probably some defect in the intermediary metabolism of pyridoxine.

In support of an intimate relation between this anæmia and pyridoxine metabolism is the fact that the biochemical disturbances characteristic of known pyridoxine deficiency (Greenberg et al. 1949) have also been demonstrated in three of five cases so investigated (see table). These disturbances involve disordered tryptophan metabolism as shown by excessive urinary excretion of xanthurenic acid and other metabolites after a loading dose of tryptophan by mouth (Greenberg et al. 1949, Harris et al. 1958). This test has not yet been performed on our patients because of technical difficulties. Abnormal pyridoxine metabolism might produce defective erythropoiesis in several ways, because in some of its actions as a coenzyme it is concerned with lipoid, nucleoprotein, and hæm synthesis. The biochemical aspects of these disturbances have been reviewed (Sherman 1950, Cerecedo et al. 1952, Schulman and Richert 1957).

It is surprising that anæmia is not usually a feature of true or conditioned pyridoxine deficiency. In infants, a pyridoxine-deficient milk diet usually caused convulsions (Coursin 1954, 1955). In adults, a pyridoxine inhibitor, 4-desoxypyridoxine, has produced dermatitis, cheilosis, glossitis, and angular stomatitis (Vilter et al. 1953). Cheilosis and angular stomatitis, which responded to pyridoxine, have been described in malnourished patients (Smith and Martin 1940). The peripheral neuritis associated with isoniazid therapy is almost certainly due to conditioned pyridoxine deficiency (Biehl and Vilter 1954). However, none of these manifestations of pyridoxine deficiency has been recorded in patients with pyridoxine-responsive anæmia.

The association of hæmochromatosis with pyridoxine-responsive anæmia in some cases (Maier 1957, Bishop and Bethell 1959, Verloop and Rademaker 1960) raises the problem of whether the anæmia precedes or follows the hæmochromatosis. If anæmia is the primary factor, then presumably the non-utilisation of iron leads to excessive iron storage with consequent hæmosiderosis which may possibly lead to hæmochromatosis. On the other hand, Bishop and Bethell (1959) suggest that excessive iron stores may impair hæm synthesis—an idea supported by the experimental work of Brown (1958). The theory that pyridoxine-responsive anæmia may occur in people with a basic tendency to hæmochromatosis is supported by the age and sex distribution. Indeed, Verloop and Rademaker (1960) adduced evidence that in their patient idiopathic hæmochromatosis may have been the primary lesion. Against this hypothesis is the fact that anæmia has rarely been recorded in primary hæmochromatosis (Sheldon 1935).

An exceptional case of pyridoxine-responsive anæmia was reported by Maier (1957). This patient's bone-marrow was megaloblastic, and there was no response to liver extract, folic acid, or vitamin B_{12}. In this connection, the marrow in our first case showed some megaloblast-like cells, and there was a definite though only partial response to both folic acid and vitamin B_{12}. In fact, even pyridoxine does not produce complete hæmatological remission, for in both our patients hypochromic red cells were still detectable even after treatment for a long time. Similar findings have been noted by others (see table).

Summary

Iron-refractory hypochromic anæmia is reported in two patients who had high serum-iron levels with increased iron stores in the bone-marrow. Both patients responded dramatically to pyridoxine therapy, and their serum-iron levels fell.

Our thanks are due to Dr. William Brockbank for referring the first case to us; to Dr. A. M. Barlow for his assistance with hæmoglobin eletrophoresis and denaturation studies; to Dr. Fred Lees for the Schilling test in the first case; to Miss J. Perry, medical illustrator, Crumpsall Hospital, for fig. 1; and to Dr. R. G. W. Ollerenshaw, director of the department of medical illustration, Manchester Royal Infirmary, for figs. 2 and 3.

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ÆTIOLOGY OF ERYTHEMA NODOSUM IN CHILDREN

A Study by a Group of Pædiatricians *

IN a retrospective investigation in Sheffield between 1951 and 1956 (Lorber and Colver 1957, Lorber 1958) it was found that of a consecutive series of 105 children with erythema nodosum 67% were tuberculin-positive.

This percentage comprised 62% who were tuberculin-positive as a result of tuberculous infection, and 5% who were tuberculin-positive as a result of B.C.G. vaccination. 46 of the tuberculin-positive children (43% of the series) had an active primary tuberculous lesion; and 10 of these later developed further tuberculous disease, in addition to the erythema nodosum and the primary complex. The only other ætiological factor detected was infection by β-hæmolytic streptococci, which was demonstrated in 10 of the 34 tuberculin-negative, and in 5 of the tuberculin-positive, children.

Unfortunately a systematic search for streptococcal infection was incomplete, especially in those who were tuberculin-positive. In 63 of 105 children throat swabs were not taken and the antistreptolysin-O titre was not estimated.

The investigation, therefore, did not necessarily show the full importance of streptococcal infection. It did show, however, that tuberculosis was becoming a less common ætiological factor than formerly. (In 1949, for example, in a comparable population Doxiadis found that of 100 children with erythema nodosum seen between 1947 and 1949 88% were tuberculin-positive and 67% had active tuberculous infection.) In view of this apparent trend it appeared desirable to carry out a prospective study.

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Material

It was planned to test for evidence of tuberculous and streptococcal infection in all patients with erythema nodosum and to search for other possible ætiological factors. In order to try and collect the greatest possible number of cases in a short time we all * agreed to investigate our cases in a similar manner. For this purpose a proforma was devised; this was completed for each patient and from it the necessary information was abstracted.

Between Jan. 1, 1957, and Dec. 31, 1959, 82 new cases of erythema nodosum were collected: 47 children were seen in Sheffield and 35 elsewhere. Children whose lesions had already faded before they attended hospital were not included in the investigation.

Method of Study

The investigations required by the plan were a tuberculin test with 1 T.U. (Mantoux) followed by a test with 10 T.U. if this was negative; a radiograph of the chest; a throat swab at the first visit; and estimation of the antistreptolysin-O (A.S.O.) titre on the first day and the eighth day after the first visit. Additional investigations, such as gastric washings in tuberculin-positive children were often performed.

In practice, tuberculin tests and X-rays of the chest were undertaken in every case, though not always according to plan, but either the throat swabs or the estimation of the A.S.O. titre were inadvertently omitted in 6 children.

An indurated area 6 mm. or more in diameter, forty-eight to seventy-two hours after the injection of tuberculin, was accepted as evidence of past or recent tuberculous infection. Active tuberculosis was diagnosed in tuberculin-positive children if there was undoubted enlargement of the hilar lymph-nodes with or without fresh pulmonary foci or areas of pulmonary collapse on the radiograph of the chest. The detection of tubercle bacilli in gastric washings or from other sources was also accepted as evidence of active tuberculosis. The finding of group-A β-hæmolytic streptococci in the throat swab, or an A.S.O. titre of 200 units or more, was accepted as evidence of recent streptococcal infection. The history of a recent sore throat was *not* accepted as such evidence.

Results

The only two ætiological factors which were discovered in the 82 children were tuberculous and streptococcal infection (table I).

A positive tuberculin test without evidence of recent streptococcal infection was found in 26 (32%). A negative tuberculin test with evidence of recent streptococcal infection was present in 33 (40%); this was the largest single group. In 15 children (18%) a positive tuberculin test was associated with a recent streptococcal infection. Altogether 50% were tuberculin-positive and 59% had had a recent streptococcal infection. No evidence of either of these or of any other infection was found in 8 (10%), but in 4 tuberculin-negative children either the throat swab or the A.S.O. titre estimations were omitted.

TABLE I—ÆTIOLOGY OF ERYTHEMA NODOSUM

Finding	No.	%
Past tuberculous infection only (old or recent)	26	32
Past tuberculous and recent streptococcal infection	15	18
Recent streptococcal infection only	33	40
No evidence of either tuberculosis or streptococcal infection	8*	10
Total	82	100

* 4 tuberculin-negative children not fully investigated.

Age, Sex, and Seasonal Distribution (table II)

11 children (13%) were under 5 years of age, 26 (32%) were between 5 and 9, and 45 (55%) were between 10 and 14. The incidence, therefore, increased with increasing age. This tendency is probably even more pronounced than is indicated by the figures, because adolescents are

TABLE II—AGE AND SEX OF PATIENTS AND SEASONAL DISTRIBUTION OF ERYTHEMA NODOSUM

—	No.	%
Age (yr.):		
0–4 11/12	11	13
5–9 11/12	26	32
10–14	45	55
Sex:		
Male	37	45
Female	45	55
Month at onset:		
Jan.-March	34	41
April-June	17	21
July-Sept.	17	21
Oct.-Dec.	14	17

not often sent to pædiatricians. There were 14 children aged 10 years and 14 aged 11 years, compared with only 3 and 4 aged 13 and 14 respectively.

There were 37 boys (45%) and 45 girls (55%). Girls predominate at all ages except 10 years and over. It is common experience that in adolescent and adult groups of patients with erythema nodosum females are in the great majority.

Erythema nodosum began in the first three months of the year in 34 (41%), in the second and third quarters in 17 each (21% each), and in the last quarter in 14 (17%).

Tuberculosis

Exactly half the children were tuberculin-positive. Table III shows that younger children were far more commonly tuberculin-positive than were older children. This contrasts with the findings in the ordinary child population. Whereas of 11 children under 5 with erythema nodosum 9 (82%) were tuberculin-positive, of 45 aged 10

TABLE III—ERYTHEMA NODOSUM: TUBERCULOUS INFECTION ACCORDING TO AGE OF PATIENTS

Age (yr.)	No.	Tuberculin-positive		Active tuberculosis	
		No.	%	No.	%
0–4 11/12	11	9	82	8	73
5–9 11/12	26	15	58	10	38
10–15	45	17	38	5	11
Total	82	41	50	23	28

or over 17 (38%) were positive reactors. In the general child population positive reactors amount to about 2% under 5 years of age and to about 20% at 10–15. The striking importance of tuberculosis as a cause of erythema nodosum in very young children is even better brought out by the finding that 73% of those under 5 had an active tuberculous lesion, compared with 30% in those aged 5–9 and only 11% in those aged 10 or over.

47 of the children in this series were seen in Sheffield. Table IV, which contrasts the findings in these with the comparable earlier series, shows that there was a progressive decline both in the number and in the proportion of positive tuberculin reactors, the proportion falling from 73% in 1951–53 to 45% in 1957–59. The proportion of active tuberculous cases fell from 55% in 1951–53 to 34% in 1954–56 and 23% in 1957–59. The number of active tuberculous cases decreased from 27 in 1951–53 to 19 in

TABLE IV—ERYTHEMA NODOSUM: PROPORTION OF PATIENTS WITH TUBERCULOSIS (SHEFFIELD CASES ONLY)

Year	No. of cases	Tuberculin-positive		Active tuberculosis	
		No.	%	No.	%
1951–53	49	36	73	27	55
1954–56	57	29	51	19	34
1957–59	47	21	45	11	23

1954–56 and to 11 in 1957–59; 8 of the 11 in the last period were under 5 years of age.

Streptococcal Infection (table V)

The most sensitive method for detecting streptococcal infections was the estimation of the A.S.O. titre, which gave positive results in 46 children (56%), whereas a positive throat swab was only obtained in 11. Evidence of a recent streptococcal infection was found in altogether 59%, although only 40% had a history of preceding sore throat. Several of those who had sore throat showed no objective evidence of streptococcal infection. Four-fifths of the tuberculin-negative children had had proven streptococcal infections, but the proportion of tuberculin-positive children in whom also a recent streptococcal infection was demonstrated was high—36%. In only 1 child under

TABLE V—ERYTHEMA NODOSUM: PATIENTS WITH STREPTOCOCCAL INFECTION

Tuberculin reaction	Total	Sore throat		Positive throat swab		High A.S.O. (200+)		A.S.O. or throat swab+	
		No.	%	No.	%	No.	%	No.	%
Positive	41	11	27	3	7	14	34	15	36
Negative	41	22	53	8	20	32	80	33	81
Total	82	33	40	11	13	46	56	48	59

5 years of age was the condition proved to be due to streptococcal infection.

Double Ætiology

The 15 children with apparent evidence of double ætiology were divided into two groups. 7 had active tuberculous lesions and their A.S.O. titres did not exceed 300 units, indicating that the more likely cause of the erythema nodosum was a recent tuberculous infection. In the other 8 no active tuberculous lesion was found; their A.S.O. titre was either 300 or more, or β-hæmolytic streptococci were still present in their throat swabs. These cases can, therefore, be regarded as of streptococcal origin, although in some the raised A.S.O. titre could have been an incidental finding (Bywaters et al. 1957, Daguet 1959).

Unknown Ætiology

No evidence of tuberculous or of streptococcal infection or of any other ætiological factor was detected in 8 children. 1 of these was tuberculin-positive as a result of

TABLE VI—ERYTHEMA NODOSUM: FINAL ASSESSMENT OF ÆTIOLOGY

Ætiology	No.		%	
Active tuberculous infection only	16		19	
Active tuberculosis and recent streptococcal infection	7	33	9	41
Tuberculin-positive, no streptococcal infection	10		13	
Tuberculin-positive, recent streptococcal infection	8	41	11	50
Streptococcal infection only	33		39	
Unknown	8		9	
Total	82		100	

earlier B.C.G. vaccination; his throat swab and A.S.O. titre were negative. The remaining 7 were tuberculin-negative; in 3 of these both the A.S.O. titre and the throat swab was also negative, but in the last 4 either one or the other of these tests was inadvertently omitted.

Final Assessment

The final assessment of the ætiology of these 82 cases is presented in table VI. In 50% the evidence favours a streptococcal ætiology, in 41% it favours a tuberculous ætiology, and in 9% no ætiological agent was discovered.

Miscellaneous Features

2 children had had recurrent attacks of erythema nodosum, and their attacks were of streptococcal origin.

This observation accords with the earlier finding (Lorber 1958) that repeated attacks of erythema nodosum occurred only in association with streptococcal infection.

Erythema nodosum in more than one member of a single family occurred in two instances. The brother of one and the mother of another affected child developed erythema nodosum within a week or two of the index case. In each of these instances the cause was tuberculosis and there was a history of recent contact with an open case of tuberculosis.

Summary and Conclusions

In children in this country the incidence of erythema nodosum due to tuberculosis is declining progressively; in children under 5 years of age tuberculosis is still by far the commonest cause, but such cases are becoming rare. Tuberculosis accounts for only a small proportion of cases of erythema nodosum in children over 10 years; of 45 cases in this group only 5 showed an active tuberculous lesion.

β-hæmolytic streptococcal infection is the commonest cause of erythema nodosum in children, except the very youngest.

In some cases a double ætiology cannot be excluded.

In most cases the ætiology can be discovered by timely and adequate investigations.

We wish to thank Dr. J. L. Emery and Miss E. Finch, who performed all the special laboratory investigations.

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AUTOIMMUNE HÆMOLYTIC ANÆMIA

Three Cases with Antibodies Specifically Active against Stored Red Cells

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THREE examples have so far been described of antibodies specifically active against stored red cells. Brendemoen (1952) demonstrated a cold agglutinin of this type, while Hougie et al. (1958) and Stratton et al. (1960) have reported stored-cell antibodies active at 37°C.

In the past 2 years we have encountered three examples of these antibodies in women between the ages of 43 and 58 years. These patients had symptoms and signs of severe anæmia, and they presented special problems in blood-grouping and cross-matching. In each case the Wassermann and Price's precipitation reactions were positive; but the *Treponema pallidum* immobilisation test, undertaken in one case, was negative, suggesting that these were false positive results associated with the anæmia.

The serum of all three patients when tested against a large panel of stored red cells, showed an unusual distribution of positive agglutination reactions which could not be correlated with any of the known antigens. In two cases the serum reacted with saline-suspended stored cells, and the third serum reacted with the same cells by the indirect antiglobulin technique. On substituting fresh cells from the same donors for the stored reacting cells, there was no agglutination.

All the patients improved with corticosteroid therapy. In two cases the stored-cell antibodies disappeared; in the third case the antibody became very much weaker, and it was active at low temperatures only.

The antibody present in the first patient was thoroughly investigated, and forms the main subject of this report. From our results, we conclude that the antigen arises during storage by the action of intracellular enzymes reacting with a basic substrate normally present in all red cells.

Case-report

This patient had been under hospital care for 3 years with cystadenocarcinoma of both ovaries, and later with carcinoma of the breast. Treatment had included oophorohysterectomy, deep X-ray therapy, and transfusion with nine pints of blood. 2 months after the last blood-transfusion, she reported as an outpatient with increasing dyspnœa and jaundice of a few weeks' duration. Her hæmoglobin was 4·5 g. per 100 ml. (34%). Her red cells showed anisocytosis and polychromatophilia, with 10% reticulocytes; spontaneous agglutination caused difficulty with cell-counting and cross-matching.

Serological Findings

The patient is group O, Cde/cde, MsNs, P_1, Lu(a−), Kell-, Le(a−b+), Fy(a+). The direct antiglobulin test on the red cells was positive, the cells being sensitised with an antibody of the non-gamma type. Initial tests at 37°C with the serum against saline suspensions of fifty group-O genotyped red-cell samples, stored for various periods in glycerol at −20°C, gave twenty-five strong positive results. The patient's fresh cells were agglutinated by her own serum; forty other samples of fresh group-O cells were all negative. The stored red cells were of known rhesus, MNS, Lutheran, Kell, Lewis, Duffy, and Kidd group systems. No correlation could be found between the reacting cell-samples and these group antigens.

Six positive results were found in testing forty-two donor blood-samples collected into acid-citrate dextrose and stored for 4 weeks at 4°C. One positive result was found in thirty clotted blood-samples stored at 4°C for 10 days.

The antibody was strongly active at 4, 12, 18, and 37°C in saline and albumin (table I). The negative stored and fresh cell-samples did not react with the patient's serum in saline or serum/albumin, and the indirect antiglobulin technique gave negative results. All tests using the patient's serum against fresh or stored enzyme-modified cells were strongly positive. The antibody was not inhibited by any secretor saliva, or by group-O non-secretor saliva. It was not inhibited by hydatid-cyst fluid, or by heating at 56°C for 30 minutes. The Wassermann and Price's precipitation reactions were both strongly positive. Her serum was not anticomplementary. The stored-cell antibody was not inhibited by Wassermann antigen, and was not absorbed by sheep cells. After complete absorption with stored cells the Wassermann reaction remained positive. The Donath-Landsteiner reaction for cold hæmolysins was negative.

It seemed possible that a plasma antigen was being adsorbed on to some cells during storage. But thirty-five samples of fresh normal serum and citrated plasma, including some from subjects whose stored cells were known to react, had no inhibitory effect on the antibody.

Against the serum we have tested saline suspensions of two thousand fresh group-O blood-samples, and, after neutralisation of the anti-A and anti-B, thirty group A and B blood-samples. All of these tests, with one exception, were negative. The exception was a sample from a normal donor whose cells were strongly agglutinated by the serum. Absorption and elution tests, together with a family study, showed that this

TABLE I—TITRATION RESULTS WITH REACTING STORED CELLS

Temperature	Dilutions of serum								
	1	2	4	8	16	32	64	128	256
12°C (saline)	+++	+++	++	++	+	+	±	−	−
18°C (saline)	+++	+++	+++	++	++	+	±	±	−
37°C (saline)	+++	+++	+++	++	++	+	+	±	−
37°C (albumin)	+++	+++	+++	++	++	+	+	+	−

TABLE II—REACTION OF ENZYME-TREATED FRESH RED CELLS WITH THE PATIENT'S SERUM

Serum	Reaction after treatment with ficin for:		
	5 sec.	20 sec.	60 sec.
Patient	−	±	+++
Control:			
Incomplete anti-D(1) ..	−	−	−
Incomplete anti-D(2) ..	−	−	−

reaction was due to a " private " antigen, the antibody for which was present in the patient's serum. The antibody was not anti- Mi^a, V^w, M^g, Wr^a, Sw^a, V, Vr, Levay, Be^a, Js^a, Kp^a, Di^a, or E^w. The serological results suggest that this antibody is not related to the stored-cell antibody present in the same serum. (This " private " antigen will form the subject of a further report.) Tests with serum from the other two cases with stored-cell antibodies were negative with the fresh cells of the donor possessing the " private " antigen.

Six hundred fresh blood-samples have been tested by enzyme techniques with the patient's serum, and all were strongly positive. Stored Bombay cells, and stored cells of the rare phenotypes i_1 and i_2 (Marsh and Jenkins 1960), were negative on direct testing with the serum but strongly positive by enzyme techniques. Twelve fresh samples of cord blood were negative on direct testing but positive by enzyme methods. Cells modified with papain, trypsin, chymotrypsin, and ficin all reacted strongly with the serum.

The degree of cell-enzyme modification necessary to produce agglutination with the patient's serum was investigated. Fresh pooled group-O rhesus-positive cells were exposed to 0·05% ficin, buffered at pH 7·3 at 37°C for various periods, washed, and tested against the patient's serum and two incomplete anti-D serum samples in parallel (table II).

Clearly only the briefest exposure to a proteolytic enzyme is necessary for activation of this cell antigen.

A series of absorption and elution tests were made using fresh untreated cells, fresh enzyme-modified cells, and reacting stored cells. Absorption for 2 hours at 37°C was followed by four washes in saline and elution into AB serum by heating at 56°C. The results show that the antibody reacting with stored cells is the same as that reacting with enzyme-modified fresh cells (table III). Further tests then showed that six absorptions with fresh untreated cells did not remove the antibody for fresh enzyme-modified cells or for reacting stored cells. Six absorptions with reacting stored cells removed the antibody for these cells, and also for fresh enzyme-modified cells. Six absorptions with fresh enzyme-modified cells removed the antibody for these cells, and also for reacting stored cells. Absorption with three different reacting cell-samples removed all antibody from the serum.

Brendemoen (1952) and Stratton et al. (1960) found that heat treatment of fresh cells caused development of the stored-cell antigen, and this we have confirmed. Fresh inactive cells heated for 30 minutes at 56°C became positive with the serum; $4^1/_2$ hours at 50°C, or about 70 hours at 37°C was needed to produce the same effect. The antigen become active after saline or serum suspensions of fresh cells were heated. Addition of sodium azide to fresh red cells before incubation at 37°C inhibited development of the antigen.

TABLE III—ABSORPTION AND ELUTION TESTS BETWEEN FRESH RED CELLS, ENZYME-TREATED RED CELLS, STORED REACTING RED CELLS, AND THE PATIENT'S SERUM

After absorption with patient's serum	Cells				Tests in
	Stored positive	Stored negative	Untreated fresh	Ficinised fresh	
Eluate from cells:					
Stored positive	++	−	−	++	Saline
	+++	+++	+++	+++	Papain
Fresh ficinised	++	−	−	++	Saline
	+++	+++	+++	+++	Papain
Fresh untreated	−	−	−	−	Saline
	−	−	−	−	Papain

Tests at 37°C.

The serological results after heating red cells at 56°C were much weaker than those obtained by enzyme methods, or after storage. Table IV shows the results of heating active stored cells at 56°C for various periods. It seems that while heating at 56°C activates the mechanism by which the antigen is produced, the antigen itself is slowly destroyed at this temperature. Heat-stability tests on fresh enzyme-treated cells were unsuccessful because the cells rapidly hæmolysed on heating.

Variation of the pH did not activate the antigen. Red cells were stored in saline, buffered to pH 5·0, 7·0, and 9·0 at 4°C and at 37°C. The antigen became weakly active at both temperatures at pH 7·0 only, shortly before the samples became too hæmolysed for further testing.

To try to correlate length of storage with antigen activity, forty-eight blood-samples, which had been stored frozen in glycerol for periods ranging from a few weeks to 26 months, were examined. About half the samples appeared to become positive with a few weeks of storage. Thereafter the others changed very slowly. Three out of six samples stored for 26 months in glycerol were negative. The antigen change has been

TABLE IV—EFFECT OF HEATING ACTIVE STORED CELLS AT 56°C

Positive stored cells	Dilutions of patient's serum							
	1	2	4	8	16	32	64	128
Unheated ..	+++	+++	+++	+++	++	+	+	±
Heated for 5 min.	+++	+++	+++	++	++	+	±	−
Heated for 10 min.	+++	+++	+++	+++	++	+	±	−
Heated for 15 min.	+++	+++	+++	++	+	±	−	−

Saline-suspended red cells. Tests at 37°C.

closely followed in several stored blood-samples, the developing antigen gradually increasing in strength. Examination of repeated samples collected from the same donors suggests that the speed with which the antigen develops during storage is a fairly constant characteristic of the individual.

Brendemoen (1952) considered that the stored-cell antigen may arise by denaturation of the receptor for incomplete cold antibodies. The reactions of active cells with complete and incomplete cold autoagglutinins was therefore studied. Fresh red cells, enzyme-treated red cells, and active stored red cells were tested against serial dilutions of serum containing complete and incomplete cold autoagglutinins. There was no correlation between the presence of the active stored-cell antigen and either increased or decreased sensitivity to these antibodies.

The serological results suggest that the antibody in this patient's serum reacts with a basic red-cell antigen usually present in fresh cells in the inactive form. The " T " antigen is of this kind, and it seemed possible that the patient's serum contained an unusual form of anti-T. The serum was, therefore, absorbed six times with fresh group-O cells, ficinised for 1 minute to remove the stored-cell antibody. Cells from the same donor were then T-activated, using a bacterial enzyme. While the patient's absorbed serum did not react with 1-minute ficin-treated cells, or with cells modified for the normal 15 minutes, it reacted strongly with the T-activated cells. Normal anti-T agglutinins are present, therefore, and the additional atypical antibody is unlikely to be an unusual form of anti-T.

Discussion

Brendemoen (1952), Hougie et al. (1958), and Stratton et al. (1960) have described antibodies which react with antigens developing within stored red cells. The serum of our three patients contained antibodies with similar specificity, and each patient had a hæmolytic anæmia of unknown ætiology. It is perhaps significant that in each case, during the hæmolytic crisis, the red cells contained the active form of the antigen, and the patient's own cells and serum reacted directly; whereas during the remissions

after treatment, the antigen became inactive in the patient's own fresh cells, although like other cells it could be activated by enzymes. The positive Wassermann and Price's precipitation reactions probably represent false results associated with the stored-cell antibody and the hæmolytic anæmia.

The antibodies here described appear to react with an antigen present in either the active or inactive form in all red cells, including the cells of infants at birth, and which is independent of other group systems, including the antigens which react with cold autoantibodies.

Certain antibodies (e.g., anti-Le^a) may react weakly with stored red cells. For this reason many laboratories make exclusive use of fresh cells for antibody detection. Unless enzyme-treated cells are included in the test panel, antibodies active against stored red cells may not be detected. Antibodies having this specificity, however, must be rare because many thousands of serum specimens have been examined in this laboratory and only these three samples have been found.

Stored-cell antibodies may be rapidly identified by replacing the stored reacting cells with fresh cells from the same donors, and further by checking that the Wassermann and Price's precipitation reactions are positive.

Summary

Three examples of antibodies showing specificity for antigens developing in stored red cells are described. The serological findings in one case are given in detail.

It is suggested that the homologous antigen is activated by intracellular enzymes from a precursor substrate which is normally present in all red cells.

The antibodies were associated with autoimmune hæmolytic anæmia, and with false positive serological reactions for syphilis in all three patients.

We are most grateful to Dr. I. E. Clark for her cooperation, and to Dr. R. R. Race and Dr. Ruth Sanger, from whom we obtained the T-activating enzyme. We are also grateful to Miss J. Mears for her technical assistance.

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STEATORRHŒA PRESENTING WITH GASTROINTESTINAL PROTEIN LOSS

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PROTEIN loss from the gastrointestinal tract has been investigated by Citrin et al. (1957), who demonstrated exudation of albumin into the stomach in a patient with hypertrophic gastritis; by Holman et al. (1959) who showed that albumin leaked into the lumen of the jejunum in granulomatous conditions, such as Crohn's disease; and by Steinfeld et al. (1957) who reported on protein loss in ulcerative colitis.

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All these workers gave ^{131}I-labelled albumin intravenously. However, protein loss via the small intestine cannot easily be demonstrated by this technique, for the albumin lost into the gut is broken down, and the constituent aminoacids and iodine reabsorbed, so that the radioactive label does not appear in the fæces (Holman et al. 1959). This difficulty was overcome by Gordon (1959), who introduced ^{131}I-labelled polyvidone (P.V.P.), a substance of high molecular weight which has the diffusion properties of albumin, but being biochemically inert is excreted unchanged in the fæces. With this substance Gordon (1959) and Schwartz and Jarnum (1959) have shown that cases of unexplained hypoproteinæmia are caused by "exudative enteropathy", a generic term suggested by Gordon (1959) to embrace all forms of gastrointestinal protein loss.

Among the causes of exudation is steatorrhœa, and cases have been described by Schwartz and Jarnum (1959), by Young et al. (1959), and by Parkins (1960).

In this paper 2 cases are described in which exudation of protein was the presenting feature of idiopathic steatorrhœa.

Methods

^{131}I-labelled P.V.P. was injected intravenously in doses of 9 to 13 μC. The fæces were collected for four days and were pooled in National dried milk tins, which fit conveniently into the counter. The fæces were made up to standard volume with water and homogenised to eliminate any geometric error. The specimens were then counted by using a ring of Geiger counters. 7 patients with diseases not affecting the gastrointestinal tract served as controls. In none of these did the fæcal excretion of radioactivity exceed 0·26% of the administered dose. These results are comparable with those of other workers (Gordon 1959, Schwartz and Jarnum 1959).

Case-reports

Case 1.—A fitter aged 44 was admitted on April 24, 1960, with a six-week history of abdominal pain and ankle swelling. Despite œdema, he complained of weight loss. He had noticed no change in his stools. Previously he had eaten a normal diet and had always been healthy. On examination the only abnormal finding was bilateral pitting œdema of the legs and ankles. There was no evidence of disease of the heart, liver, or kidneys. He weighed 153 lb.

His plasma-protein levels when first seen were: albumin 2·8 g. per 100 ml., and globulin 1·1 g. per 100 ml. As the causes of the hypoproteinæmia and œdema were not known, the following special investigations were performed:

(1) Fæcal excretion of intravenously injected ^{131}I-labelled P.V.P was 10·9% of the administered dose (13 μC).

(2) A barium small-bowel meal showed clumping of barium in the whole of the small intestine.

(3) In a peroral jejunal-biopsy specimen, subtotal villous atrophy with excessive infiltration of the mucosa by inflammatory cells was seen.

(4) The hæmoglobin level was 97%.

(5) In a five-day fat-balance test, fæcal excretion was 6·3 g. per day on a diet containing 60 g. fat per day.

(6) In a xylose-excretion test, 2 g. of the xylose was found in the urine in the first five hours after ingestion. (Normal: $6{\cdot}5 \pm 1{\cdot}2$.)

After admission the œdema disappeared and the protein level rose steadily. But, despite this apparent improvement the patient continued to lose weight long after all the œdema had gone, and his weight had fallen to 124 lb. by July 11. Because of this it was decided to give the patient a gluten-free diet. His weight thereafter increased, parallel with improvement in general wellbeing. A second jejunal biopsy was carried out during this phase of improvement, on Aug. 5, and the specimen did not differ from the first. In a second estimation of P.V.P. excretion on July 1, 0·7% of the dose was recovered from the fæces. When last seen as an outpatient on Sept. 29 he was fit and well, and weighed 154 lb. (clothed).

Case 2.—A housewife aged 35 was admitted on August 18, 1960, with a history of abdominal pain for four months and ankle œdema for six weeks. Only in the three days preceding admission had she noticed loose motions. She had previously eaten a normal diet and had always been healthy. On examination there was œdema of the legs and ankles, but no evidence of disease of the heart, liver, or kidneys. She weighed 84 lb.

Results of plasma-protein estimation when she was first seen were: albumin 2·6 g. per 100 ml., globulin 1·8 g. per 100 ml. Her hæmoglobin-level was 94%. As in the previous case further investigations were carried out.

(1) Fæcal excretion of intravenously injected ^{131}I-labelled P.V.P. was 2% of the administered dose. (10 μC.)

(2) Barium small-bowel meal (Raybar) showed dilatation of the small intestine compatible with the malabsorption syndrome, but no evidence of a localised lesion.

(3) In the peroral jejunal-biopsy specimen, subtotal villous atrophy with excessive infiltration of the mucosa by inflammatory cells was noted.

(4) In a five-day fat-balance, fæcal excretion was 11·4 g. per day on a diet containing 60 g. fat per day.

Xylose excretion was not tested.

After admission the œdema subsided, but the diarrhœa persisted. In the light of our experience with the other patient, a gluten-free diet was prescribed. A laparotomy was performed by Mr. H. E. Lockhart-Mummery three months later after five episodes of transient intestinal obstruction. A stenosis midway down the jejunum was resected. On histological examination subtotal villous atrophy with an area of local submucosal inflammatory swelling and superficial ulceration was observed. There was no evidence to suggest Crohn's disease.

Discussion

It seems probable that both these patients had idiopathic steatorrhœa, for, in addition to excessive fæcal fat, in the jejunal biopsies the typical appearances of subtotal villous atrophy were seen. The response of the first patient to a gluten-free diet was definitive. The second patient showed all the features of idiopathic steatorrhœa during the P.V.P. study. The subsequent development of a jejunal stenosis has obscured the response to a gluten-free diet, so that final proof of a gluten-enteropathy is lacking.

In both patients the episode of hypoproteinæmic œdema was the first sign of disease. There were no symptoms before this, and no history to suggest cœliac disease in childhood. Furthermore, both cases had a normal blood-picture when first seen. This suggests that idiopathic steatorrhœa may start with an episode of exudative enteropathy.

Although the intestinal lesion of idiopathic steatorrhœa is well defined, the stage reached by the clinical syndrome when the lesion develops is unknown. There is rarely any history to point to an inflammatory episode that could have altered the intestinal mucosa. Acute jejunitis is almost unknown in this country. The best description is by Hertzberg (1954), who reported 50 cases. These were acute abdominal emergencies with a high mortality; and it seems unlikely that our 2 patients had this syndrome, as the onset in them was gradual. It is noteworthy, however, that in 4 of Hertzberg's patients hypoproteinæmia and œdema developed. It seems most plausible that the exudation of protein in our patients was a manifestation of an abrupt onset of intestinal inflammation, proceeding to atrophy and steatorrhœa.

Summary

2 patients with steatorrhœa presenting as exudative enteropathy are described.

Idiopathic steatorrhœa may start with an episode of exudative enteropathy.

We should like to thank Mr. W. F. Clapham, and the staff of the Radioactive Isotope Laboratory for their assistance, Prof. E. P. Sharpey-Schafer, for permission to publish the second case-report, and Mr. J. R. Mallard, of Hammersmith Hospital, for supplies of radioactive P.V.P.

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FATAL MYCETOSIS DUE TO CANDIDA ALBICANS AFTER COMBINED STEROID AND ANTIBIOTIC THERAPY

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DURING the past 30 years blood-borne fungal infections have been recorded increasingly often under various circumstances. They have arisen:

1. As spontaneous infections (Smith and Sano 1933, Pasternak 1942, Miale 1943, and Morris et al. 1945).
2. From self-venepuncture among drug addicts (Joachim and Polayes 1940, and case 1 of Zimmerman 1950).
3. After sulphonamide therapy (Wessler and Browne 1945).
4. After long-continued antibiotic therapy, e.g., with penicillin, streptomycin, and the broad-spectrum antibiotics (Grekin et al. 1950, Gausewitz et al. 1951, Kunstadter et al. 1952, and Schaberg et al. 1955).
5. With intravenous fluid medication, although antibiotics were also being given (Duhig and Mead 1951).
6. With anti-folic-acid substances and other marrow-depressant drugs (Zimmerman 1950, Craig and Farber 1953, and Rankin 1953—apparently the first British report).
7. After operation, when the patient's defences are below normal (Caplan 1955, Davis et al. 1956, Koelle and Pastor 1956, Braude and Rock 1959).
8. With steroid therapy, as predicted by Antopol and Quittner (1952), and as reported by Craig and Farber (1953), Levy and Cohen (1955), Zimmerman (1955) cases 2 and 3, and Conn et al. (1959). An increase in superficial moniliasis during combined steroid and antibiotic therapy was reported by Bratlund and Holten (1954).

Among these reports are only two in which the patients have recovered (Wessler and Browne 1945, and case 3 of Schaberg et al. 1955). In most cases where full bacteriological and mycological studies were made, either during life or post mortem, *Candida albicans* was the causal agent.

Despite the numerous reports cited above, many still believe that *Cand. albicans* causes only superficial infection of skin or mucosæ. We therefore report a further fatal case of disseminated *Cand. albicans* infection affecting an adolescent who had been given steroids, antibiotics, and intravenous fluids.

Case report

A 17-year-old girl was admitted to the Western Infirmary, Glasgow, on Oct. 23, 1959, during her fourth attack of an acute rheumatic illness which had necessitated inpatient treatment in various hospitals for a total of 21 months in the preceding

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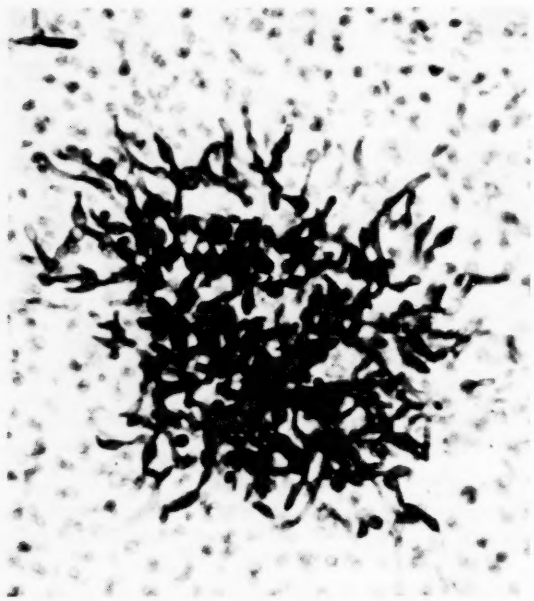

Fig. 1—*Cand. albicans* granuloma in the lung. (Periodic-acid/Schiff and hæmalum. × 495.)

8 years. The main clinical features were fever and polyarthralgia (transient and fleeting), affecting chiefly the knees, shoulders, and elbows. During her first attack pericarditis was suspected; and, more recently, short apyrexial episodes of odd behaviour and mental confusion had been noted, together with nuchal rigidity, opisthotonus, extensor spasms, and extensor plantar responses on one occasion. Her erythrocyte-sedimentation rate (E.S.R.) was generally over 100 mm. in the 1st hour. Owing to vomiting, salicylate therapy was never effective, but until the present attack the response to steroids (corticotrophin, cortisone, prednisolone) had been good.

Examination.—She was slim, pale, afebrile, and rather immature. Blood-pressure 90/70 mm. Hg; pulse regular; heart sounds normal, with no murmurs. No abnormality was found in the skin and joints, nor in the respiratory, alimentary, and central nervous systems.

Investigations.—E.S.R. 156 mm. in the 1st hour (Westergren); hæmoglobin (Hb) 49% (7·1 g. per 100 ml.); white blood-cells (W.B.C.) 4100 per c.mm.; blood-film hypochromic with normal white cells and platelets. Plasma-fibrinogen 0·84 g. per 100 ml. Anti-streptolysin "O" titre 125 units per ml. on four occasions. Throat swab: mixed growth of β-hæmolytic streptococci (later reported ungroupable) and coagulase-positive staphylococci. Blood-cultures and examinations for lupus-erythematosus cells negative. Electrocardiogram (E.C.G.): left-axis deviation with a P–R interval of 0·2 seconds. X-ray of chest normal.

Progress and Treatment

An exacerabtion of acute rheumatism was provisionally diagnosed, and treatment was started with intramuscular penicillin and with calcium aspirin 5 g. per day, which gave a mean serum-salicylate level of 26 mg. per 100 ml. (i.e., about 10 mg. per 100 ml. below the desired figure [Coburn 1943]). During the 1st week the patient had a high intermittent fever with several rigors and periods of odd behaviour, including mutism and irritability. There was a peculiar absence of sweating. The E.C.G. now showed sinus tachycardia, with marked ST depression throughout. Because the Hb had fallen to 42% (6·2 g. per 100 ml.) 2 pints of packed red cells were transfused. Aspirin and penicillin were both stopped (streptococcus ungroupable). Her condition deteriorated rapidly, and acute tonsillitis developed, with severe cervical lymphadenitis, patches of oral thrush, and an erythematous purpuric eruption mainly on the forearms and buttocks. The W.B.C.s were now 550 per c.mm. with severe granulocytopenia (though platelets were present), while a further throat swab grew coagulase-positive staphylococci and *Cand. albicans*. On the basis of sensitivity tests a regimen was instituted of fluids, erythromycin, and hydrocortisone intravenously, tetracycline intramuscularly, vitamins and nystatin by mouth.

After 3 days she became afebrile, the tonsillitis and adenitis subsided considerably, and the W.B.C. rose to 2500 per c.mm. The culture of a further throat swab was free from staphylococci, and the E.C.G. was normal. Prednisolone by mouth (40 mg. per day) was substituted for hydrocortisone. Improvement was only shortlived: a hectic remittent pyrexia recurred, with severe dysphagia, signs of peripheral and pulmonary œdema, abdominal distension, and diarrhœa. Cultures of fæces were uninformative. Because the Hb was 37% (5·5 g. per 100 ml.), a further transfusion of 2 pints of packed red cells was given. By the end of a week she was completely disorientated and incontinent; hyperpyrexia, coma, opisthotonus, and extensor spasms ensued, and she died on Nov. 14.

Postmortem Findings

Intense pharyngitis and œsophagitis, with ulceration. The stomach showed two subacute ulcers in the pyloric canal on the greater curve (probably cortisone induced), and melæna was present throughout the alimentary tract. The lungs, myocardium, liver, spleen, and kidneys contained diffusely distributed punctate pale yellow abscesses, of 1–2 mm. diameter, generally surrounded by a narrow hæmorrhagic zone. The distribution throughout both lungs was similar to that

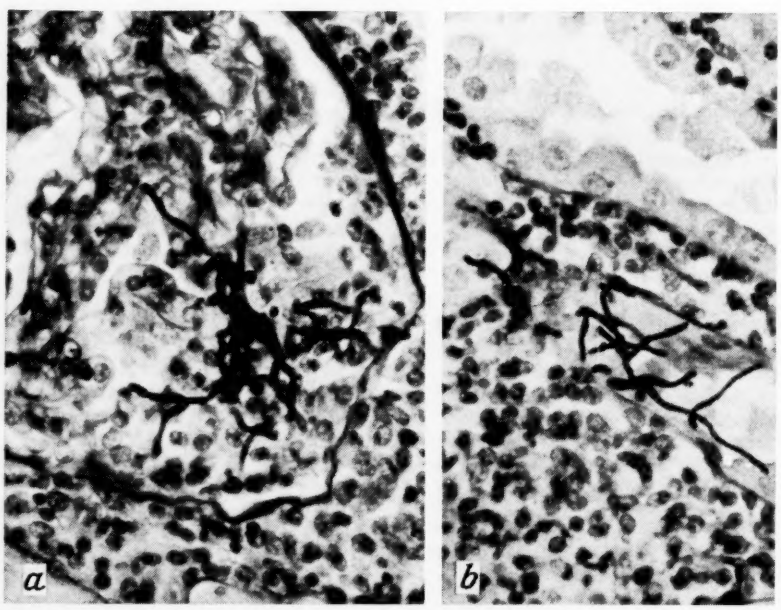

Fig. 2—Earlier fungal granulomata in relation to (*a*) a renal glomerulus, and (*b*) a renal tubule. At this stage the cellular response is predominantly mononuclear. (P.A.S. and H. 495.)

Fig. 3—Mycelial filaments in a cerebral hemisphere, with no cellular response as yet. (P.A.S. and H. ×495.)

in miliary tuberculosis, suggesting hæmatogenous dissemination of infection rather than bronchogenic spread. The parietal pericardium was diffusely adherent to the heart, which was small, with normal valves, chordæ tendineæ, and coronary arteries. The brain and all other viscera appeared normal.

Histology.—Granulomata (or abscesses) were present in the cerebral cortex, vertebral marrow, thyroid gland, and one adrenal gland, as well as in the organs already mentioned (figs. 1 and 2). Each consisted of a central mass of radiating septate mycelial filaments, unstained and refractile in sections stained with hæmatoxylin and eosin, but strongly gram-positive and positive to periodic-acid/Schiff. Numerous terminal and intercalary spindle-shaped vesicular swellings were present. Yeast forms were scanty. Surrounding the colonies was an intense polymorph and mononuclear response. In addition, however, there were younger lesions, and occasional fungal filaments could be seen in the tissues without any cellular response (fig. 3). The granulomata were about 5 days old. The lungs showed patchy pyogenic bronchopneumonia, some recent and some older, undergoing resolution or organisation. Poorly staining possibly degenerating gram-positive intracellular cocci were present. The heart revealed no valvular abnormality, but the appearances of the myocardium, although not conclusive, were compatible with those of healed myocardial Aschoff bodies (fig. 4). As well as fungal granulomata in the cerebral cortex, there was also a mild diffuse pia-arachnoid reaction composed of large mononuclear cells. No mycelial filaments were present, however, in the subarachnoid space. The vertebral marrow was very cellular, with intense plasmacystosis (more advanced than that described by Nicoll et al. [1958], and similar to that described by Aherne [1958]), and with retarded maturation of the erythroid and myeloid series. Megakaryocytes were present, and stainable iron was absent.

Bacteriology and mycology.—Dr. I. R. W. Lominski, of the university department of bacteriology, Western Infirmary, and Dr. J. C. Gentles, of the department of mycology, Glasgow University grew a pure culture of fungus from the spleen, and this was identified as *Cand. albicans*.

Discussion

The postmortem and histological findings in the heart are enough to substantiate the clinical diagnosis of recurrent atypical acute rheumatism, but some unusual features remain.

The complete absence of valvular disease of the heart is unexpected considering the number and severity of previous attacks, although the 1960 report of the rheumatic fever working party of the Medical Research Council and American Heart Association shows that the status of the heart at the start of treatment is the most important factor in determining the incidence of rheumatic heart-disease.

The disturbances of behaviour are more difficult to explain. They were not constantly associated with the administration or withdrawal of steroid therapy. Histological evidence of metastatic cerebral lesions of bacterial or fungal nature during earlier episodes was not found, while the sequence of events rules out the fungal granulomata of her terminal illness as a cause. The patient was a rather unstable and dependent child in whom a long-continued febrile illness might produce such features. Alternatively, these episodes may possibly represent a milder form of cerebral rheumatism, which in its most florid form (Osler 1898, Stockman 1920) is accompanied by hyperpyrexia, and is usually fatal.

Previous attacks did not respond to salicylate, because of intolerance, and it seems unlikely that therapeutic blood-levels were attained. Even in her terminal illness, the levels were lower than expected from the dose given; this is attributable to an increased rate of degradation of the drug.

Agranulocytosis is not known to be associated with rheumatic fever, or with the administration of penicillin or aspirin. It has been recorded in conjunction with steroid therapy (Thiersch et al. 1952, Snively et al. 1953, Rokseth 1960), and the patient was having prednisolone immediately before her transfer to this infirmary. On the other hand, she had previously had cortisone and predni-

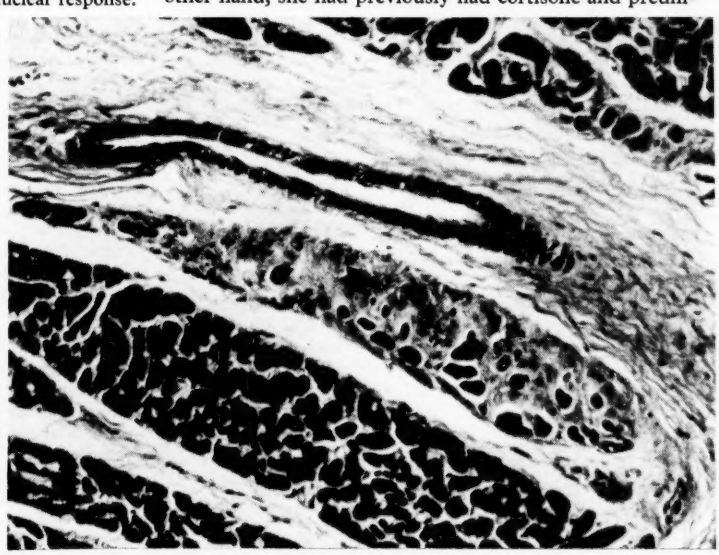

Fig. 4—Interstitial juxta-arteriolar spindle-shaped fibrotic area incorporating stray atrophic myocardial fibres, which is compatible with a healed Aschoff body. (Mallory's trichome method. ×270.)

solone in high dosage for long periods without ill effect; and, moreover, steroids are used in the treatment of agranulocytosis induced by drugs (Whitby and Britton 1957).

The clinical features of this patient's terminal illness suggest a septicæmia. Considering all the evidence, we think that during an exacerbation of acute rheumatism an upper respiratory infection and low-grade staphylococcal bronchopneumonia developed. Agranulocytosis (cause unknown) permitted a detrimental spread of the staphylococcal infection, and probably of candida also. The energetic measures which were adopted controlled the former, but later deterioration was the result of systemic dissemination of *Cand. albicans*—a fatal "iatrogenic" complication.

Finally, under steroid therapy latent tuberculous foci may be reactivated and dissemination may result (Hart and Rees 1950, Spain and Molomut 1950, Kleinschmidt and Johnston 1951, Mackinnon 1959), while Levy and Cohen (1955) reported a mixed fungal and bacterial disseminated infection in relation to corticotrophin therapy. It became necessary to examine the lesions bacteriologically and histologically for evidence of other organisms, but none was found.

Summary

A case of mycetosis due to *Candida albicans* was associated with long-continued steroid therapy and intensive antibiotic therapy.

The patient, a 17-year-old girl, had recurrent acute rheumatic fever. Salicylates were vomited persistently; the response to steroids had been dramatic during her first attack 8 years earlier, but each relapse responded less satisfactorily. Her terminal illness presented as a further relapse. The therapy given was designed to counteract complications, including agranulocytosis, anæmia, and a severe staphylococcal infection, but it proved ineffective.

We are greatly indebted to Prof. D. F. Cappell, and to the late Dr. James Reid, for their encouragement and guidance in the preparation of this paper.

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MULTIPLE CONGENITAL ANOMALY ASSOCIATED WITH AN EXTRA AUTOSOME

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THE association of congenital anomaly in man with an extra autosome was first described by Lejeune et al. (1959), who reported the finding of trisomy for chromosome number 21 (Denver) in mongolism. Two female infants with multiple anomalies have been described by Patau et al. (1960) with trisomy for one of the medium-sized acrocentric chromosomes. The same workers have reported six infants, trisomic for number 18, with a different group of congenital abnormalities including low-set and malformed ears, a small mandible, flexion deformities of the fingers, anomalies of the feet, ventricular septal defect, spasticity with probable mental defect, and diverticulum of the small intestine (Smith et al. 1960). Edwards et al. (1960) reported an infant with many similar clinical features who was trisomic for number 17. He has since studied two more similar patients (Edwards 1961).

The case of an infant with several features similar to those of the patients of Edwards and Patau, who were trisomic for chromosome 17 or 18, is reported here.

Case-report

Clinical Features

The infant, a girl, was born in July, 1960, at University College Hospital.

Her mother and father were aged 40 and 49 years respectively at the time of her birth. They are both healthy persons of normal intelligence. The mother had had one previous miscarriage. A brother of 8 years and a sister of 4 years are normal. There is no consanguinity in the family. A first cousin of the propositus is a mentally backward child with several congenital abnormalities, whom it has not been possible to study.

The patient was a mentally defective infant with peculiar facies characterised by bilateral ptosis, shallow orbits, low-set malformed ears, a small receding mandible, and a small mouth. There was scaphocephaly with the parietal width greater than the frontal width. The cranial sutures were not widened. Neck webbing was noted, and the chest was flattened. There were no deformities of the hands or fingers. Clinical dextrocardia was confirmed by electrocardiography. In the lower limbs there was bilateral mobile talipes calcaneo-valgus, bilateral short hallux, and slight limitation of abduction of the left hip.

From the second day the patient had cyanotic attacks after feeds, and a systolic murmur was heard. Attacks of respiratory distress with tachypnœa and cyanosis led to increasing tachycardia and liver enlargement. Tube-feeding was necessary from the first day, the swallowing and sucking reflexes being impaired or absent. Slight spasticity of the legs also developed. Despite antibiotic treatment, oxygen, and digitalisation, the patient's condition deteriorated and she died sixty days after birth.

Necropsy

Dextrocardia with a left-sided aortic arch and a large ventricular septal defect, 1 cm. across, were found. The pulmonary artery and aorta both arose from the right ventricle. The ventricular septal defect formed the only outlet from the left ventricle.

The left kidney was hydronephrotic with a hydroureter; no obvious cause for this was apparent.

The falx cerebri was deficient anteriorly, but the brain was normal.

The lungs showed bronchopneumonia.

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TABLE I—CHROMOSOME COUNT OF PATIENT AND PARENTS

Subject	No. of chromosomes				
	<45	45	46	47	>47
Patient	0	1	2	25	0
Mother	0	1	20	0	0
Father	0	0	12	0	0

The figures represent numbers of cells.

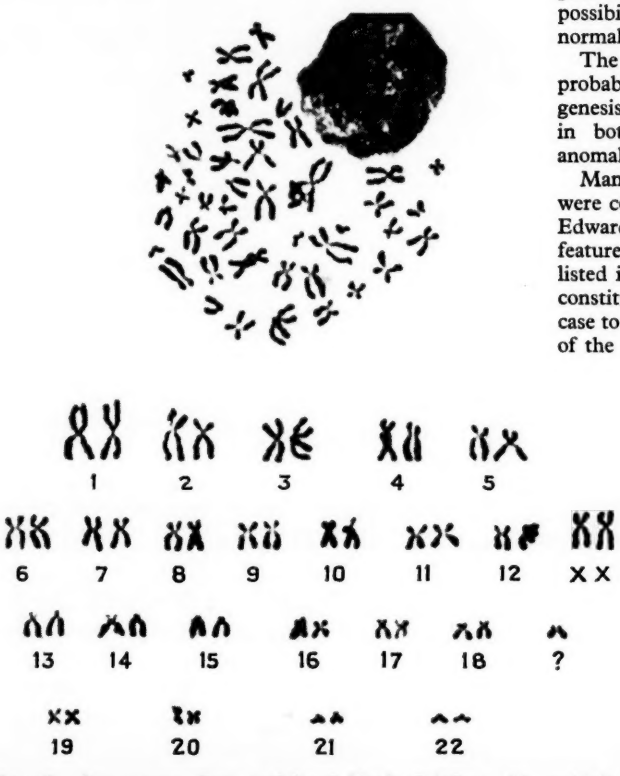
Cytology

A buccal smear showed nuclear sex-chromatin bodies in 32% of cells. No multiple sex-chromatin bodies were seen in any cell.

Chromosome studies were carried out on peripheral blood by a modification of the technique of Hungerford et al. (1959). Squash preparations showed a great majority of cells with 47 chromosomes (table I). Counts other than 47 can probably be attributed to breakage of cells or other technical artefacts.

Detailed analysis of four cells showed an XX sex-chromosome constitution and an extra autosome in the 17–20 size range (see accompanying figure). The additional chromosome varies a little in size from cell to cell. It appears to be slightly smaller than a number 18 but clearly larger than 21 or 22. The centromere is subterminal as in 17 and 18, not metacentric as in 16, 19, and 20. The short arms approximate to those of 17 or 18, while the long arms are shorter than those of 18 and longer than those of numbers 19 or 20 or the small acrocentric chromosomes.

The chromosomes of the mother and father have been studied from peripheral blood by the method of Moorhead et al. (1960). The results of counts on these are also shown in table I. Detailed analyses of suitable cells from the mother and father showed normal karyotypes for both.



Somatic chromosomes from peripheral blood of infant with multiple congenital anomalies.

Discussion

The chromosome count and analyses on this infant show no evidence of mosaicism, the great majority of the cells having 47 chromosomes and, in those analysed, a constant karyotype. The extra chromosome cannot be matched with any of the normal pairs. The finding of a normal female sex-chromatin pattern in the buccal smear makes it probable that this chromosome is an autosome and not a deleted X chromosome; moreover, in the cells analysed the short arms of the X are longer than even the long arms of the additional chromosome. Detailed analysis suggests that the karyotype most likely represents trisomy of 17 or 18 with partial deletion of the long arms. The presence of 47 rather than 46 chromosomes excludes the possibility of a reciprocal translocation in an otherwise normal constitution.

TABLE II—CLINICAL FEATURES COMMON TO CASES OF TRISOMY IN THE 17–20 RANGE

Feature	Edwards et al. (1960) (trisomic 17)	Smith et al. (1960) (trisomic 18)		Present case (trisomic ?)
		Case 8	Case 19	
Low-set, malformed ears	+	+	+	−
Anomaly of eyes or eyelids	−	−	+	+
Small mandible	+	+	+	+
Small or triangular mouth	+	−	−	+
Mental defect	+	+	+	+
Webbing of the neck	+	?	?	+
Cranial deformity	+	+	+	+
Deficiency of the falx cerebri	+	?	?	+
Chest deformity	+	+	+	+
Ventricular septal defect	+	+	+	+
Patent ductus arteriosus	+	+	+	−
Flexion deformity of fingers	+	+	+	−
Short hallux	+	−	−	+
Syndactyly of toes	+	−	+	−

The trisomy and the postulated deletion in this case probably arose by primary non-disjunction during gametogenesis in one of the parents. The normal karyotype found in both parents excludes an inherited chromosome anomaly.

Many of the abnormalities described in this infant were common to those in the three infants described by Edwards et al. (1960) and by Smith et al. (1960). The features common to two or more of these four patients are listed in table II. It seems reasonable to regard these as constituting a syndrome with no greater variation from case to case than is found in mongolism. The consistency of the clinical findings in these patients is reinforced in further cases trisomic for chromosomes 17 and 18 studied by Edwards (1961) and Patau (1961) respectively.

From the data of these two groups of workers there seems no reason to doubt the identity of the chromosome involved in each group of patients. Nor is there any reason to doubt that the chromosome involved in the present case differs from those in the other two groups of cases. In view of the apparent chromosomal specificity of the trisomy in mongolism, it has been previously thought that each of the 22 theoretical types of autosomal trisomy would be associated with a clinically distinct syndrome (Smith et al. 1960, Patau et al. 1960). Now that Ferguson-Smith and Handmaker (1961) and other workers have observed that both chromosomes 21 and 22 are satellited the specificity of the mongol trisomy has become uncertain. The

group of cases into which the present case fits provides stronger evidence that trisomy of different autosomes may give rise to the same or very similar clinical pictures. If this is so the effects of autosomal trisomy cannot be entirely due to direct gene dose effects, but must be at least partly due to an indirect distortion or imbalance of the factors controlling growth associated with the additional chromosomal material present. The fact that the affected chromosomes in the group of cases under discussion fall within a narrow range of morphologically similar chromosomes further suggests that certain human chromosomes may be homeologous.

Summary

A case is presented of an infant with multiple congenital anomalies including low-set ears, a small mandible, mental defect, deficiency of the falx cerebri, webbing of the neck, ventricular septal defect, and bilateral short hallux. These were associated with the finding of an extra autosome in the 17–20 size range.

The clinical features in this case correspond closely with those in reported cases trisomic for chromosomes 17 or 18.

This work was carried out during tenure of a grant from the British Empire Cancer Campaign. I am grateful to Dr. B. E. Schlesinger for permission to publish studies on this case.

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HORMONE EXCRETION, DIET, AND PHYSIQUE IN SOMALIS

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So far as we can ascertain, there have been no previous investigations of this kind on Somalis (nomadic shepherds of the Juba heights).

Materials and Methods

Our studies were made on a group of thirteen men aged between 22 and 52. They were all in good health; they made their living as shepherds; and their diet was confined to camel's milk, wild berries, and, now and then (perhaps twice a month), kid's meat.

The investigations were:

1. Measurement of lower-limb/trunk ratio (Viola, 1933), blood-pressure levels, and body-weight, and assessment of anatomical sexual characters.

2. Determination of the daily urinary excretion of total neutral 17-ketosteroids (method of Holtorff and Koch, 1940) and of catecholamines (method of Burn and Field, 1956).

3. In eight cases, chromatographic fractionation of the 17-ketosteroids of the urine, by the method of Dingemanse et al. (1946), as modified by Devis (1951) and Albeaux-Fernet et al. (1954).

4. Determination of the electrophoretic pattern of the serum-proteins.

The biological material was kept at temperatures not exceeding 5°C, the portion to be used for quantitative determination of the catecholamines being immediately acidified with concentrated hydrochloric acid. The determinations were carried out within a week of obtaining the sample.

TABLE II—CHROMATOGRAPHIC FRACTIONATION OF THE TOTAL URINARY NEUTRAL 17-KETOSTEROIDS

Case no.	I	II	III	IV	V	VI	VII	VIII	Total (mg. per 24 hr.)	Total 17-ketosteroids*
1	1·240	1·320	0·541	0	0·294	0·598	0·294	0·072	4·379	3·85
2	0·980	0·832	1·610	0·538	0·538	0·980	0·784	0·832	7·094	6·71
3	0·060	0·055	0·680	0·970	0·970	0·970	1·000	0·920	4·78	4·21
4	0·336	1·680	5·88	0·756	0·336	0·672	0·924	0·084	10·66	8·92
5	0·260	0·320	0·410	0·950	1·250	1·050	0·980	1·250	6·47	5·73
6	1·100	0·650	0·350	0·650	0·800	1·000	0·550	0·200	5·30	4·18
7	1·800	0·900	1·210	0·960	0·520	0·800	0·430	0·650	7·27	5·98
8	0·920	0·260	0·520	0·850	0·960	0·260	0·420	1·130	5·32	4·80

* Holtorff and Koch (1940)

The results are set out in the tables.

The lower-limb/trunk ratio was constantly raised; the facial, axillary, and pubic hair were scanty, though development of the testes was normal; and the systolic blood-pressure only once reached 140.

A low value was found for the urinary excretion of the total neutral 17-ketosteroids (average 5·6 mg. per twenty-four hours, as against 9–13 mg. for Caucasians living in Italy). There was no constant relation between the degree of androgenuria and the normality of the external genitals (volume and consistence of the testes, in particular). Urinary excretion of total catecholamines was low (average 154 μg. per twenty-four hours, as against the 200–540 μg. reported as normal for Caucasians). The results of

TABLE I—CLINICAL AND METABOLIC DATA

Case no.	Age (yr.)	Weight (kg.)	Lower-limb/trunk ratio	Hair					External genitals		Blood-pressure (mm. Hg)	Total 17-keto-steroids in urine (mg. per 24 hr.)	Total catechola-mines in urine (μg. per 24 hr.)	Proteinæmia	
				Head	Beard	Eye-brows	Axillary hair	Pubic hair	Penis	Testes				Total (g. per 1000 ml.)	Albumin/globulin ratio
1	45	57	113/40	+++	+−−	+++	+−−	+−−	+++	+++	110/80	3·85	190	5·80	1·08
2	23	55	117/42	+++	+−−	++−	+−−	+−−	+−−	+−−	120/80	6·71	175	6·00	0·85
3	25	55·5	106/43	+++	+−−	++−	−−−	+−−	+++	+−−	140/100	4·21	140	5·65	0·88
4	40	60	110/47	+++	+−−	+++	+−−	+−−	+++	+++	125/96	8·92	180	5·50	0·61
5	25	54	110/52	++−	+−−	+++	+−−	+−−	+++	++−	120/80	5·73	215	5·48	0·96
6	30	47	105/45	++−	+−−	++−	+−−	+−−	+++	+++	130/100	4·18	120	6·10	1·04
7	52	47	109/46	++−	++−	++−	+−−	+−−	+++	+++	120/70	5·98	156	5·30	0·69
8	23	50	108/50	++−	−−−	+−−	+−−	+++	+−−	+−−	135/90	4·80	85	5·30	0·66
9	22	56	111/44	+++	+−−	++−	++−	+−−	+++	+++	120/100	9·70	135	5·40	0·68
10	50	55	108/42	+++	+++	+−−	++−	++−	+−−	+−−	105/70	5·15	225	6·05	0·49
11	34	50	100/50	+++	+−−	++−	+−−	+−−	+++	++−	115/80	6·00	174	5·5	0·69
12	40	48	96/47	+++	+−−	+−−	+−−	+−−	+−−	++−	115/75	3·95	110	6·20	0·69
13	50	47	108/50	++−	+−−	++−	+−−	+−−	+−−	+−−	100/65	4·65	98	6·30	0·81

+++ = well developed; ++− = moderately developed; +−− = poorly developed; −−− = absent.

chromatographic fractionation of the neutral 17-ketosteroids in the urine contrasted with the virtually constant steroid androgenic components of predominantly testicular origin (fractions v and iv). The dehydro-isoandrosterone level was increased only in the cases with the highest urinary 17-ketosteroids (cases 2 and 4). The proportions of the 11-oxy-17-keto compounds excreted were normal.

Electrophoretic study of the protein pattern gave a slightly decreased value for the total proteins; this was often associated with inversion of the albumin/globulin ratio, mainly due to increased globulin. There was no significant correlation between the degree of abnormality of the protein pattern and of the urinary androgen composition.

Summary

In a group of Somali shepherds we found a low urinary excretion of total 17-ketosteroids and total catecholamines. Steroid compounds of testicular origin were always present in the urine.

No significant correlation was found between the hormonal metabolism, the development of the external genitals, and the abnormal protein pattern.

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Preliminary Communications

ASSAY OF VITAMIN B_{12} IN BLOOD

A Simple Method

THE term "saturation analysis" has been given to a form of microassay which has recently been used in measuring the blood levels of insulin [1 2] and thyroxine.[3] The method seems to be applicable to the assay of other compounds of biological importance, and our purpose here is to illustrate its use in the estimation of plasma-vitamin-B_{12}.

Vitamin B_{12} in blood is normally largely bound to a specific carrier protein [4]; but if exogenous vitamin is added in amounts corresponding to two or three times the normal physiological level the protein-binding sites become saturated and excess vitamin remains in free form.[5] The distribution of the exogenous vitamin in plasma between bound and free moieties is quantitively dependent upon the amount of vitamin that has been added. Moreover, using a single sample of plasma, a "calibration" curve may be plotted relating the concentration of exogenous compound to the distribution in the two fractions (expressed as the "free" to "bound" ratio—i.e., Rf/b). This curve may in turn be used to measure unknown amounts of vitamin which have been extracted from plasma specimens presented for assay.

Fig. 1 illustrates the principle of the method as applied to the estimation of vitamin B_{12} in blood. Vitamin labelled with one of the radioactive isotopes of cobalt is added to the plasma to be assayed (the "test" plasma), and thus performing two distinct functions:

1. It provides information about recovery of endogenous vitamin from the test plasma throughout the extraction procedure.

2. It permits evaluation of the ratio Rf/b (given by the distribution of radioactivity between the two fractions).

The activity of the added material must clearly be such that acceptable count-rates are obtained at succeeding stages of the assay; but for greatest accuracy in the final result the weight of labelled vitamin added should be as small as possible compared with the weight of the endogenous vitamin which is to be estimated. The sensitivity of the technique is thus largely determined by the specific activity of available labelled vitamin B_{12}.

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5. Miller, A. *J. clin. Invest.* 1958, **37**, 536.

METHOD

1 mμg. of ^{57}Co-vitamin-B_{12} (Abbott Laboratories, U.S.A.; specific activity 1·7 μC per μg.) in physiological saline was added to about 5 ml. of the plasma under investigation. Radioactivity introduced into the specimen was assayed in a well-type scintillation counter, correction being made for sample volume.[6] After about 30 minutes' equilibration, the pH of the plasma was adjusted to 4·5 with acetate buffer, and the sample was heated for a further 30 minutes in a bath of boiling water Precipitated proteins were separated by centrifugation and washed with 2–3 ml. of acetate buffer (pH 4·5), and the washings and supernatant were combined and taken down to about 1 ml. under reduced pressure. Recovery of vitamin in the extract was estimated at this stage by counting in the well-scintillation counter.

To the concentrated extract 0·5 ml. of a "standard" plasma was added. At the same time 0·5 ml. aliquots of the same standard plasma were added to amounts of labelled vitamin B_{12} ranging from 0·5 to 5·0 mμg. The whole group of specimens was allowed to equilibrate for 2 hours before being transferred to dialysis bags cut from 18/32 in. 'Visking' tubing, and then each made up to about 3 ml. with physiological saline and dialysed against 300 ml. of saline for 48 hours.

Activity remaining in the bags after dialysis was estimated in the well counter, and the free-to-bound ratio was calculated from the expression:

$$\mathrm{Rf/b} = \frac{\mathrm{Cr} - \mathrm{Cb}}{\mathrm{Cb}}$$

where Cr = counts placed in dialysis bag, and Cb = counts remaining in bag after dialysis.

Values of Rf/b from the calibration samples were plotted against the exogenous vitamin-B_{12} content of each sample (fig. 2) and the exogenous vitamin content of the unknown specimen derived by interpolation of the corresponding value of Rf/b on the resulting curve. The vitamin content of the

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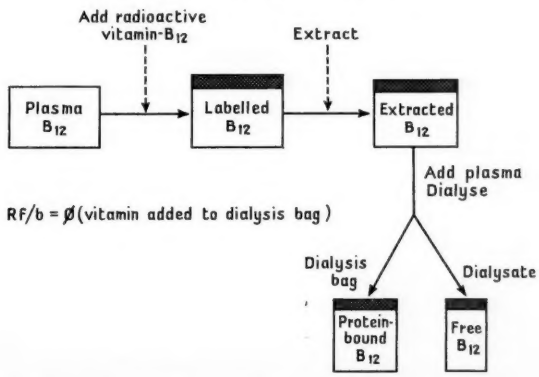

Fig. 1—The principle of saturation analysis as applied to the assay of vitamin B_{12}.

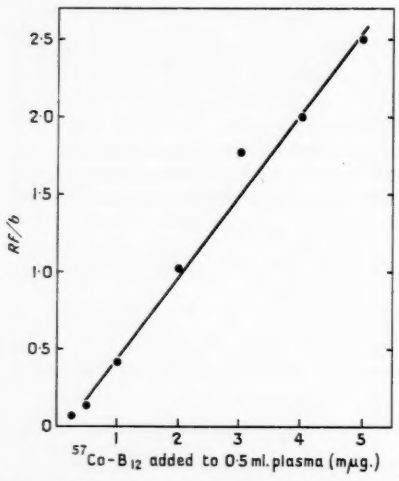

Fig. 2—Calibration curve relating Rf/b to exogenous vitamin-B_{12} level in a specimen of plasma.

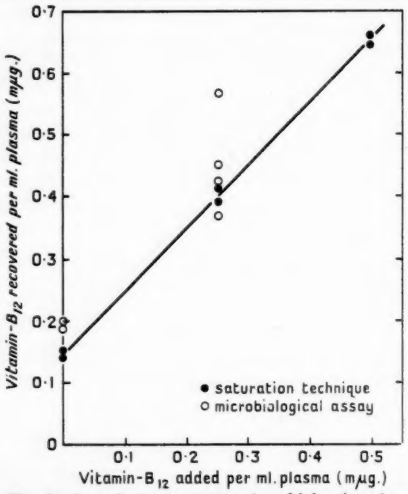
Vitamin-B_{12} recovered per ml. plasma (mμg.)
Vitamin-B_{12} added per ml. plasma (mμg.)
● saturation technique
○ microbiological assay

Fig. 3—A typical experiment in which vitamin-B_{12} was added to plasma before assay.

original sample of test plasma was finally calculated from the expression:

$$\text{Vitamin-}B_{12}\text{ concentration} = \frac{Ca}{V}\left(\frac{B}{Cr} - \frac{1}{S}\right) \text{ mμg. per ml.}$$

where Ca = counts added to the test plasma (counts per sec.), V = sample volume (ml.), B = weight of vitamin derived by interpolation from calibration curve (mμg.), Cr = counts recovered in extract (counts per sec.), and S = specific activity of ^{57}Co-vitamin B_{12} (counts per sec. per mμg.).

RESULTS

To test the method experiments similar to that represented in figure 3 were performed. Known amounts of unlabelled vitamin were added to aliquots of selected plasma before assay, and the samples were then analysed by both "saturation" and microbiological techniques.

Repeated assays on samples of the same serum showed variations of the order of 5%; one such series of six repeat determinations (a bank serum) gave a mean value of 420 μμg. per ml., with a standard deviation of ±23 μμg.

Plasma specimens from twelve normal subjects were assayed, and their values ranged from 330 to 840 μμg. per ml., with a mean of 626 μμg. This compares with a range of 270 to 1200 μμg. per ml. found by a microbiological technique.[5] The results from these subjects and from a number of patients (in some of whom normal values for plasma-vitamin-B_{12} were expected) are shown in the table.

DISCUSSION

Preliminary results with the saturation technique have shown great constancy, suggesting that a reliable routine method based on these findings may emerge. The method is simple both in principle and application, and makes little demand on technical resources other than those normally found in the radioisotope laboratory.

A potential source of error which we have not investigated in this study depends upon the possibility of competition by compounds other than vitamin B_{12} for the binding sites of vitamin-B_{12}-binding protein. Such competition would enhance displacement of the vitamin into the free moiety, and cause overestimation of the amount present. The overall agreement with microbiological results suggests that errors arising from this source have not been significant.

Using material with a specific activity of 1·7 μC per μg., and 3–5 ml. of plasma, we have obtained results down to the levels found in pernicious anæmia, which would be useful clinically. But ^{58}Co-vitamin B_{12}, of activity greater than 12 μC per μg., is available, and thus much greater sensitivity than we have achieved in this study is, in principle, attainable.

PLASMA-VITAMIN-B_{12} LEVELS IN NORMAL SUBJECTS AND VARIOUS PATIENTS

Disease	No. of samples	Range per ml. serum (μμg.)	Average	S.D.	Coefficient of variation
Normal subjects	12	330–840	626	±141	22%
Plasma III*	6	390–450	420	± 23	5·6%
Pernicious anæmia	3	11–74	49	..	..
Vegans	4	75–234	158	..	..
Steatorrhœa	1	400	..	..	..
Postgastrectomy status	1	248	..	..	..
Folic-acid deficiency	1	257	..	..	..
Myxœdema	1	528	..	..	..
Chronic myelogenous leukæmia	1	9900	..	..	..
Chronic lymphatic leukæmia	1	580	..	..	..
Chronic lymphatic leukæmia with renal disease	1	4410	..	..	..
Carcinoma of urogenital tract	5	295–660	500	..	..

*Same specimen of bank plasma assayed on different occasions.

SUMMARY

A simple isotopic method is described for the estimation of vitamin-B_{12} levels in blood.

Preliminary results of assays with normal plasma and with plasma taken from patients with various pathological conditions are presented and compared with values obtained by a microbiological technique.

It gives us pleasure to acknowledge the encouragement given by Prof. J. E. Roberts and Dr. E. S. Williams, and the help of Dr. A. D. Smith and Dr. J. W. Stewart who performed microbiological assays and provided us with specimens of plasma.

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ACUTE LEUKÆMIA AND KLINEFELTER'S SYNDROME

LEUKÆMIA is occasionally associated with chromosomal abnormalities [1–6]; and, in mongolism,[7–11] where the autosomal count is abnormal, the incidence of leukæmia is higher than usual. We have seen a case of Klinefelter's syndrome with acute leukæmia and a sex-chromosome

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Fig. 1—Chromosome preparation from culture of peripheral blood.

abnormality. As we know of no other recorded association of these states, we present this report.

CASE-REPORT

A single man, aged 36, was admitted to hospital with painful swelling of his right leg. He had had no significant illnesses previously. He was an only child and the family history was non-contributory.

He had never experienced puberty, and, despite androgen therapy, he had only scant body hair and had never shaved oftener than once a week. Because of this he was seen in 1956 at Bellevue Hospital, New York, where Klinefelter's syndrome was diagnosed, and bilateral mastectomy was done for gynæcomastia. At this time testicular biopsy showed peritubular fibrosis and no spermatogenesis. His neutrophil polymorphs showed a male "drumstick" pattern, and his follicule-stimulating hormone (F.S.H.) levels were positive to 52 mouse units. (For fuller report see Briggs and Kupperman.[12])

He was acutely ill, being febrile, with severe cellulitis of the right lower leg. He was obese, 65 in. tall, and 33½ in. from heel to pubis. Body-hair distribution was female. He had a small phallus, and both testicles, though less than 1 cm. in diameter, were fully descended. The only other unusual finding was moderate splenomegaly.

A diagnosis of acute myelogenous leukæmia was suggested by the peripheral blood-count, and confirmed by bone-marrow aspiration. Despite treatment with antimetabolites, steroids, and antibiotics his illness ran a hectic febrile course, complicated by sepsis and acquired hæmolytic anæmia. He died 28 days after admission.

12. Briggs, D. K., Kupperman, H. S. *Amer. J. Med.* 1958, **24**, 915.

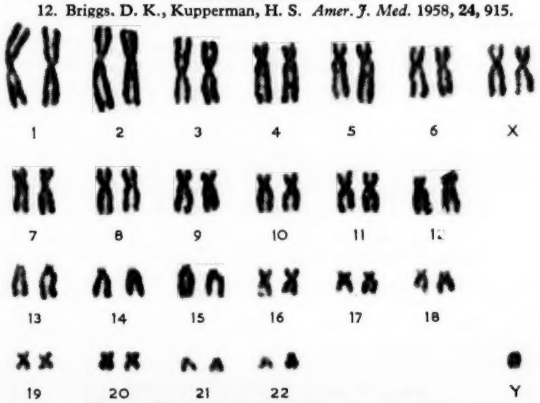

Fig. 2—Idiogram of the chromosome pattern.

Before treatment we were able to culture the peripheral blood. All sixteen cells counted showed 47 chromosomes, with the additional chromosome in the 6–12 range (Denver nomenclature [12]) being most likely an X chromosome. Buccal smears revealed a positive sex-chromatin pattern. The F.S.H. level was again positive to 52 mouse units.

DISCUSSION

This man undoubtedly had Klinefelter's syndrome with an abnormal (XXY) sex-chromosome pattern, but we do not know whether the acute leukæmia was associated with this syndrome by chance or otherwise.

A background of autosomal abnormality has been shown in both acute and chronic leukæmia, but no alterations of sex-chromosome pattern have been described in these conditions. In mongolism, where the clinical picture is clear, and the incidence of leukæmia is higher than usual, an extra autosome has been found.

One example can hardly give grounds for supposing that *any* extra chromosome—be it sex chromosome or autosome—predisposes to leukæmia; or that our finding of Klinefelter's syndrome and leukæmia was anything but fortuitous. We present this case, however, as an addition to the still incomplete information about chromosome abnormalities, and to provoke others to report similar or related states.

We are grateful to Dr. N. C. Webb, Dr. T. Kushnick, and Dr. J. H. Tjio for aid and encouragement in this study.

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Medical Societies

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

Vector of *Hepatocystis kochi*

AT a meeting on June 15 Prof. P. C. C. GARNHAM gave an account of the hunt by him and his colleagues, R. B. Heisch and D. M. Minter, for the vector of *Hepatocystis kochi*, the common parasite of African monkeys, which is closely related to the malaria parasites.

The parasite is well known and common; its sexual forms are present in the blood, but its transmission remained a mystery. No vector could be clearly suggested on geographical grounds alone—the infection does not occur in New World monkeys; but, since it does occur throughout tropical Africa, especially in the common vervet monkey, *Cercopithecus æthiops*, and in very varied climatic conditions, only a few insects (tsetse flies and simulium, for instance) could be excluded on distribution alone and there remained a multitude of other possibilities. Mosquitoes, sandflies, culicoides, ticks, mites, and other arthropods from the forest environment of the monkeys were suspected, and direct examination and feeding experiments were carried out on an extensive scale, but were all negative. There were too many apparently potential vectors for there to be any clear incrimination of one.

Then from Canada there came a report that hæmoproteus of birds could develop in culicoides, and Professor Garnham began more strongly to suspect that midges of this group might

similarly be the vectors of hepatocystis though tests hitherto had been negative. *Culicoides adersi*, common on the Kenya coast where infected monkeys are also common, were caught and fed on the monkeys, and sporozoites were eventually found in their salivary glands, but without proof that they were sporozoites of *H. kochi*. Clean monkeys inoculated with these sporozoites usually remained negative, but one, which was flown to England, developed parasitæmia after two months. This strongly suggested that culicoides was responsible, but the stage between infection of culicoides and the appearance of sporozoites in its salivary glands remained unknown. With malaria parasites the oocysts are present in the stomach wall of the mosquito, but in culicoides no similar structures could be found during ordinary dissection. Attention was therefore turned to specimens of culicoides which had been fixed whole and sectioned—to the whole midge, in fact, and not merely to its gut—and it was then observed that oocysts were present—but, unexpectedly, in the hæmocoele, not in the stomach wall. The ookinete within the gut lumen is evidently so vigorous, unlike the ookinete of the malaria parasite, that it penetrates the basement membrane and escapes to develop in the body cavity, and from there the sperozoites make their way to the salivary glands. The final proof of identity came when the specific *H. kochi* pigment was found in the oocysts, and the chain was shown to be in fact complete.

The implications of this careful and successful hunt, which occupied much time and energy, seem to be important: when the evidence pointed strongly to culicoides the failure to find the essential link in the stomach wall of the insect was only overcome when the team began to doubt the preconceived idea that that was where it should have been. This fact may be relevant in other circumstances.

Reviews of Books

The Practical Management of Head Injuries

JOHN M. POTTER, F.R.C.S., consultant neurosurgeon, Manchester Royal Infirmary, and clinical lecturer in neurosurgery, University of Manchester. London: Lloyd-Luke (Medical Books). 1961. Pp. 75. 12*s*.

THIS might have been a pedestrian book, but it is so well written that he who runs may read—and will probably remain to saunter through its pages. It is directed at the general surgeon, general practitioner, casualty officer, and senior nurse; it is full or practical help on first-aid, nursing, surgical management (e.g., when, if ever, to do a lumbar puncture), the recognition of complications, and the decision when to deal with the case in the nearest operating-theatre and when to transfer it. Two small points may be mentioned: convulsions are less likely in children than in adults to denote significant local damage or compression; and the advice regarding urgent or deliberate treatment of a fracture involving a venous sinus might be made more clear. If hæmorrhage from a sinus is encountered the skull defect can be quickly enlarged. While finger pressure is applied from below, bone should be ripped off *both* sides of the sinus, and this should make it possible to suture muscle over any tear. In the absence of hæmorrhage, however, a chip found sticking into a sinus should preferably be left until the patient is transferred to a neurosurgeon. This charming and invaluable little book should be extremely popular. It is surprisingly complete, well indexed, sound as a bell, and much needed in every hospital in the country.

A Modern Introduction to the Family

A Sociological Analysis of the Family, its Relationship to Society and its Contributions to Personality. Editors: NORMAN W. BELL, EZRA F. VOGEL. London: Routledge & Kegan Paul. 1961. Pp. 691. 60*s*.

THE authors, both of them connected with Harvard's Laboratory of Social Relations, have collected more than 50 papers about the modern family, particularly the modern American family. The three main parts are concerned with the sociological analysis of the family as a family; the family's relationship to society; and the family's contribution to personality.

In an introductory essay the editors point out that during the 20th century comfortably situated families have gradually recognised the existence of problems of personal and sexual adjustment and have been turning for help to expert sources outside the family. On the whole, research into family difficulties has not been related to general theory so much as to practical questions. For instance, in marriage counselling, child guidance, and "education for marriage" there is enormous public demand for advice on family matters. Attempts to meet these demands have often led to the neglect of more theoretically significant research and a relatively uncritical acceptance of the research that has been done.

Depression and the late war led to a broader view by drawing attention to the intimate relationship between the family and contemporary external social systems. But such studies were usually approached from the standpoint of adjustment and happiness of individual members of a family or of individual families. Typically, they concentrated on the family response to a particular crisis. No attempt was made to treat systematically the relationship between the family and external social systems.

This book tries to bring together studies which have tried to deal with the family as a social system. They are concerned with the relationship between the family and external systems and also between the family and the individual.

It is often said that the family is declining but the evidence in this book suggests that this is not so. The extended family with all its ramifications has perhaps declined in importance but the nuclear family is becoming increasingly specialised and to some extent is stronger than ever before. For instance, certain of its functions have recently increased; the care of infants, household maintenance, and the management of individual tensions are now almost exclusively its province, where before they were performed largely by the extended family or the community.

The implications of this are here discussed from every conceivable angle. The book also contains interesting accounts of the attempt to abolish the family in Russia just after the Revolution, the position of the family in the Israeli *kibbutzim*, and the Nayar who, in a period before the British control of India, were supposed not to have a true family system and so to belie the theory that the family is universal.

Factors Controlling Erythropoiesis

JAMES W. LINDMAN, M.D., associate professor of medicine, North Western University Medical School, Chicago; FRANK H. BETHELL, M.D., late professor of internal medicine, University of Michigan. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 208. 66*s*.

THIS volume in the American Lecture Series is a comprehensive and balanced account of the historical development of ideas and of present views on the importance of humoral factors in the control of red-cell formation and production. The authors have themselves contributed to research on this subject and a brief account of this work is included. They begin with a remarkably illuminating short account of the development and functions of the red cell; then they review the evidence about the influence of endocrine glands on erythropoiesis. This evidence all suggests that endocrine influence is secondary, so the bulk of the book is devoted to the experimental search for other humoral factors. These factors have been detected by the effect of plasma preparations on the blood-count and bone-marrow of rodents, especially the rat; describing the methods, the authors deplore their length and laboriousness, but admit that nothing more satisfactory has yet been developed. In a long chapter the chemical, physical, and physiological properties that have been assigned to humoral plasma factors are described and the often

conflicting results of researches in different laboratories are critically discussed.

The resemblance of the properties of batyl alcohol to those of one of the humoral factors is appraised in another chapter. Discussing the possibility that the kidney may produce a humoral erythropoietic factor, the authors remark that this is almost the only site at which there is positive evidence of its formation. Finally there is a short chapter about the evidence for the presence of humoral erythropoietic factors in man, which have been most clearly demonstrated in polycythæmia vera. The bibliography is notably complete, there is a good index, and the book is well produced.

Linman and Bethell admit that " areas of disagreement and controversy currently characterise this field of hematologic research ". But enough is known to suggest that humoral factors do help to control red-cell formation.

I Could a Tale Unfold

Violence, Horror and Sensationalism in Stories for Children. P. M. PICKARD. London: Tavistock Publications. 1961. Pp. 228. 25*s*.

CONCERN about the effect on young people of violence, horror, and sensationalism in comics, films, and television programmes grows as the incidence of juvenile delinquency and crimes of violence rises. This book is topical and particularly welcome for a wide view of the problem both historically and psychologically.

Miss Pickard is well-qualified to write such a book: she is a trained Froebel teacher; she has been headmistress of an experimental school for children aged 4–11 years; she has a degree in psychology, has undergone a full psychoanalysis, and trained in child guidance at Guy's Hospital. Since 1944 she has trained teachers of young children, first at her own college and then for two years in the Control Commission of Germany; she is now in charge of the only group of graduate men and women taking a Froebel course for primary teaching.

The book contains many interesting facts, particularly about the history of children's comics, both here and in America, and about the historical sources of many contemporary children's stories. Elsewhere the book is rather disappointing. Unsubstantiated generalisations are common: for instance, the definition of art whets the appetite but does not satisfy it. Art is defined as " A means of communication of experience, between human beings, not necessarily involving language, in which traditional and novel elements are blended so as to stimulate simultaneously 'high' (intellectual) and 'low' (not-conscious) levels of the mind, typically by a rhythmic or equivalent pattern-like construction ". But this idea is not developed. Many interesting statements are made without supporting evidence. It is, for instance, suggested (p. 94) that all children become mentally ill without enough of the right tales and that imbalance in the mental diet results in greed. Again these ideas are not expanded.

But few will disagree with Miss Pickard's conclusion. In assessing what it is that children require of us, Miss Pickard says: " They want good stories and they want them well told."

The Disabilities and Injuries of Sport

Sir ADOLPHE ABRAHAMS, M.D., F.R.C.P. London: Elek Books, 1961. Pp. 95. 12*s*. 6*d*.

IN his youth Sir Adolphe was a well-known runner and oarsman. For many years he has been an honorary medical officer of the Amateur Athletic Association, and, as an adviser to the International Board, has accompanied Britain's team to the Olympic Games and elsewhere. Few men are so well qualified to write on the injuries of sport, and in this very practical book, he has done a valuable service to his colleagues who are periodically asked to discharge similar, but less responsible, duties.

Whether a volume which lists so many serious hazards to sportsmen can be recommended to the participants themselves is more doubtful. The chapter headings (Tenosynovitis, Myositis Ossificans, Danger of Heat-stroke) recall the famous anatomical diagram showing how many muscles a golfer uses when making a shot, with the caption " Don't look at this. Show it to your opponent."

The illustrations are not quite so good as the text. In fig. 4 the postulated scaphoid fracture is not at all easy to see. The only ankle injury depicted—an avulsion of the calcaneal tuberosity—is an uncommon one; and, by mishap, fig. 3, in the title of which a " mallet finger " is described as causing a hyperextension deformity, shows a dislocated thumb. These matters are easily corrected to make this a first-class manual.

Life, Death and the Law

A Study of the Relationship Between Law and Christian Morals in the English and American Legal Systems. NORMAN ST. JOHN-STEVAS. London: Eyre & Spottiswoode. 1961. Pp. 363. 35*s*.

IN his discussion of a number of contemporary problems from both legal and moral viewpoints, the author, who is a Catholic, is concerned with both English and American legal systems and with Christian morals, both Catholic and Protestant. He begins with law and morals and the distinctions and connections between them. Later chapters are devoted to birth control, artificial human insemination, human sterilisation, homosexuality, suicide, and euthanasia. The history of the legal position of each of these subjects and the attitudes towards them in English and American law and in the Christian churches is discussed and copiously documented. This will make the book a valuable work of reference for many years to come.

Many controversial moral issues on which there is an urgent need to formulate legal policy are discussed. Should the sale and distribution of contraceptives be restricted by law? Ought the state to foster sterilisation policies? What should be the attitude of the law to artificial insemination? Should homosexual acts in private between consenting adults be subject to the criminal law? Should euthanasia be permitted by the law? Ought suicide and attempted suicide to be treated as criminal offences? The one serious omission is abortion, which is scarcely mentioned.

The publishers say this book will be of interest not only to lawyers but also to historians, theologians, sociologists, and moralists. To this list should certainly be added doctors, many of whom will find this a very readable and absorbing work.

Medical Evidence in Personal Injury Cases

DOROTHY KNIGHT DIX, Q.C.; ALAN H. TODD, M.S., B.SC., F.R.C.S., emeritus orthopædic surgeon, Croydon group of hospitals. London: H. K. Lewis. 1961. Pp. 242. 42*s*.

A FEATURE of the post-war years has been a big increase in litigation concerning personal injuries, and there are now very few doctors in this country who are not called on from time to time to investigate and assess an accident claim. Some indeed have created a new specialty in this work. For the most part these men are scrupulously impartial, and the " insurance doctor " who would minimise the complaints of an amputee by dilating upon the excellent function of his remaining limbs has, it is to be hoped, disappeared for ever.

But clashes of opinion over the medical aspects of a case are still common. Often they arise because doctors and lawyers have different viewpoints and have been differently trained. Until now the only technical literature they have had in common has been the medical reports on a particular case. Miss Dix and Mr. Todd are to be commended, therefore, for producing a book of great service to both professions. It contains, for the doctor, advice on the examination of claimants, the writing and agreeing of reports, and his demeanour in the witness-box. For the lawyer there are chapters on the special aspects of injuries in different regions, and on the significance of various medical terms. These latter sections, some medical readers may feel, are rather too detailed for easy comprehension by their legal colleagues. Certainly Mr. Todd has been very

dogmatic on some points. Arbuthnot-Lane's rigorous "no-touch" technique for orthopædic operations is seldom practised in its original form today. To stigmatise (p. 93) anything less as negligent is to condemn the work of many leading surgeons. Some notes on the limitations of radiography would have gone a long way towards dispelling the widely held view that an X-ray can resolve all diagnostic problems. Hand injuries figure so often in industrial accidents that they merit a separate chapter in later editions. These are minor criticisms of a volume which goes a long way towards filling a need of doctors and lawyers.

Techniques in Tropical Pathology

B. G. MAEGRAITH, F.R.C.P., professor of tropical medicine, W. E. KERSHAW, M.D., professor of parasitology and entomology, D. DAGNALL, chief technician and demonstrator in parasitology, Liverpool School of Tropical Medicine. Edinburgh: Oliver & Boyd. 1961. Pp. 164. 25*s*.

THE Liverpool School of Tropical Medicine has done a considerable service to all doctors and their associates in the tropics by producing this brief and concise account of any laboratory techniques they may require. The descriptions are easy to understand and may be followed without difficulty by the non-pathologist doctor and certainly by every laboratory technician. The techniques recorded include not only the usual examinations for parasites or for abnormal hæmoglobins but also illustrated advice on how to obtain skin and muscle specimens for the diagnosis of filariasis, leprosy, and trichinosis. Most of the illustrations are excellent, but the picture of sickle cells and one of the two plates dealing with malarial parasites are not up to the general high standard. The book is immensely practical, and one of its valuable features is an appendix on basic laboratory equipment. This contribution by the Liverpool School will be a lasting success.

Milk: the Mammary Gland and Its Secretion

Editors: S. K. KON, A. T. COWIE, National Institute for Research in Dairying, Shinfield, Reading, England. New York and London: Academic Press. 1961. Vol. I. Pp. 515. 100*s*. Vol. II. Pp. 423. 86*s*.

THIS two-volume work is probably the most comprehensive account of the biology of the mammary gland that has ever appeared, and the editors are to be congratulated on assembling authoritative reviews from experts of international repute.

The first volume describes the morphogenesis, structure, and growth of mammary tissue, and of human lactation in all its phases; and there follows a discussion of hormonal induction of lactation and galactopoiesis in farm animals, and detailed chapters on the biochemistry of mammary glands including protein metabolism, the biosynthesis of lactose, and the formation of milk fat.

The second volume deals with nutritional aspects. The nutrition of the lactating woman is discussed in the light of information from dietary surveys, and the requirements in terms of energy, protein, calcium, iron, and vitamins are outlined. The food requirements of lactating farm animals (ruminant, mare, and sow) are reviewed in the light of the differences in the architecture of their digestive tracts and the role which micro-organisms play in the fermentation of proteins and carbohydrates. The metabolic "diseases" associated with lactation (milk fever, grass tetany, and ketosis) and their possible causes are described. After an account of the dietary needs of lactating rats and other laboratory animals, four chapters are devoted to the nutritional value of milk: they deal with the chemical and physical properties of milk, an evaluation of human and cow's milk in infant nutrition, lactation in relation to the growth of offspring, and immunological aspects of colostrum.

It is stated that "perhaps the most significant characteristics of human milk are its special physical properties that permit it to form soft and easily digestible curd in the alimentary tract of the infant; its high protein value for growth attributable to the perfect balance in proportions of the essential amino acids which it contains; the emulsified small fat globules and the proportion of unsaturated fatty acid of low molecular weight, which contribute to physiological well-being; the uniqueness of the carbohydrate, lactose and carbohydrate containing compounds; and the amount and distribution of the vitamins and minerals best suited for the synthesis of the necessary rich protoplasmic composition of the very young organism and its rapid growth and development and for satisfying its high energy requirements".

This encyclopædic work will be of great worth to clinical, biochemical, physiological, and veterinary workers. Full references are given chapter by chapter and the standard of production of the volumes is excellent.

The Physiological Basis of Medical Practice (7th ed. London: Baillière, Tindall & Cox. 1961. Pp. 1554. 128*s*.).—The latest edition of Best and Taylor is an undoubted improvement. This time many authors have written sections on their specialty, and, as before, discussion of the physiology of a system is followed by paragraphs on disorders of that system. The type used for subheadings catches the eye well, and the placing of references at the end of each chapter is far easier for the reader than hunting at the end of the book. Moreover, references in their proper context are more likely to tempt the reader to sample some of them. Most figures are well reproduced and good, but some of them are scratchy and unpleasing, and those taken from photographs are the least successful. But some will say that a few poor figures are more easily borne than an increase in price. Our congratulations to Prof. C. H. Best and Prof. N. B. Taylor on once again producing a textbook which is sure to be in demand.

The Queen Charlotte's Textbook of Obstetrics (10th ed. London: J. & A. Churchill. 1960. Pp. 533. 50*s*.).—The text of this popular undergraduate book by members of the clinical staff of the Queen Charlotte's Maternity Hospital, London, has been widely revised and new material added. There is a short but effective account of emotional disorders in pregnancy; and the healthy baby, the premature baby, and the sick baby are described in a way that the student and young graduate will find very helpful. Intragastric oxygen is recommended in the treatment of asphyxia neonatorum, though there is now convincing evidence that little or no oxygen reaches the systemic circulation by this method. In a comparison between male and female brim shapes, the male is said to be typically triangular; but it now seems clear that the brim shape in a healthy male is indistinguishable from that of a female. The book is well produced with many excellent illustrations.

New and Nonofficial Drugs 1961 (Philadelphia: J. B. Lippincott. London: Pitman Medical Publishing Co. Pp. 849. 30*s*.).—This annual publication of the Council on Drugs of the American Medical Association contains descriptions of drugs generally available in the United States which have been included in the *U.S. Pharmacopeia*, the *National Formulary*, or *New and Nonofficial Drugs* for not longer than 20 years. A useful innovation in the index to the 1961 edition is the addition of the maker's name, and a cross-reference to the approved name against all entries of proprietary names.

Geoffrey Keynes: *Tributes on the Occasion of his Seventieth Birthday*. (London: Rupert Hart-Davis for the Osler Club of London. 1961. Pp. 64. 20*s*.)—This elegant book records the tributes paid to Sir Geoffrey Keynes at the party at Saint Bartholomew's Hospital and at the meeting of the Osler Club which were both held in his honour on March 26, 1957. The list of his writings given at the end of the book, compiled by Mr. W. R. Le Fanu, amply justifies the claims made by his friends in the earlier pages for Sir Geoffrey's skill with the scalpel and with the pen.

THE LANCET

LONDON 1 JULY 1961

Complicating the Chromosomal Anomalies

FOR most of us the four main original syndromes of chromosomal anomaly remain sufficient—XXY (Klinefelter's syndrome), 21-trisomy (mongolism [1]), XXX, and XO (Turner's syndrome)—to list them in probable order of frequency. The picture has been set out in LENNOX's general account.[2] Complications of this picture are of two kinds—variations on the original four (which are numerous), and new syndromes involving other chromosomes.

Turner's syndrome in particular is becoming a most fascinating labyrinth, as is made clear by a report from Edinburgh [3] on primary amenorrhœa. From the practical point of view the main importance of the Edinburgh work was its demonstration that a very high proportion of cases of primary amenorrhœa—possibly half (and very much more than half in those of short stature)—are due to chromosomal anomalies: a strong pointer to the need for cytological investigation of all such cases. Of the 14 Edinburgh cases that fell more or less into the Turner's category, only 5 were of straightforward classical XO Turner's syndrome. 4 had one normal and one abnormal X chromosome (no 2 of the 4 showing the same abnormality) and 5 were mosaics—2 XO/XY, 2 XO/XX, 1 XO/XXX, and 1 XO/XYY. Mosaics have been reported in several other recent accounts—XO/XY [4 5] and XO/XX [6] for instance—and there are rumours of yet more complex combinations to come. (It is sobering to recall how much disbelief FORD's[7] early claims for the existence of mosaics excited.)

VAHARU et al.[8] reported Turner's syndrome with one normal X and one minute chromosome which they believed to be part of a Y. 2 of JACOBS et al.'s [3] cases had incomplete Xs. Most interesting of the abnormal Xs is the isochromosome type, of which at least 5 examples have been reported.[3 9 10] (An isochromosome is one in which the two arms are exact duplicates of each other.) In the cases concerned there is a normal total of forty-six chromosomes: there is one X, no Y, and an additional large chromosome very like a no. 3. Abnormalities of the sex-chromatin suggest that this additional chromosome is an isochromosome formed by the union of two X long arms. Effectively, then, such a patient has the long arms of three Xs, but the short arm of only one: it must be deduced that the absence of the second short arm is enough to induce Turner's syndrome.

The bulk of the facts still accords with the view that the development of a normal gonad demands that all or nearly all the cells which form it be either pure XX or pure XY. If any substantial part of the cells forming it contain less than the whole of both chromosomes, the gonad will be imperfect: it is perhaps unnecessary at this stage to inquire too closely why sometimes the imperfect gonad should be nearly non-existent, and sometimes form some elements of testis or ovary or both. In any case it has not enough endocrine function in the fœtus (or at puberty) to induce proper sexual development, and the characteristic woman-like neuter of Turner's syndrome will appear, by operation of the familiar Jost fœtal-castration mechanism. So much is reasonable. But the details are hard to fill in. No-one has achieved a satisfactory full correlation of the associated stigmata of Turner's syndrome and the precise chromosomal anomaly involved in each case (though JACOBS et al.'s evidence that stature resides in the short arm of the X seems good). Such cases as those of CHU et al.[11] (plain XY, yet plainly Turner's) and BLOISE et al.[12] (XO, yet with at least more masculinity than most) or those of OIKAWA and BLIZZARD [13] are very hard to fit into any simple picture. The syndrome, or constellation of syndromes, remains full of problems.

The Klinefelter-syndrome group is not yet so intricate, but it is heading in the same direction. There are XXXY forms,[14 15] XXXXY forms,[16] XXYY,[17] and mosaics.[18] The more complex anomalies add to the basic syndrome of XXY Klinefelter's syndrome a variety of defects. Whether these additional defects are specific is not yet clear. The simple presence of additional chromosome material beyond the normal seems always to be associated with a tendency to congenital defects of various common kinds, and it is difficult to disentangle specific lesions from this purely quantitative effect. (The report by Mr. MAMUNES and his colleagues, on p. 26 of this issue, of leukæmia in XXY Klinefelter's syndrome raises an interesting new theme. If this is a genuine association, one can begin to assume that all chromosome anomalies, and not only 21-trisomy, may tend to produce leukæmia. But, as these workers recognise, a single case of association of two such common conditions means nothing—yet.)

Outside the sex chromosomes and no. 21, only one chromosome anomaly has so far been identified as presenting a defined clinical syndrome: This is trisomy-17 (trisomy-13 [19] is expected to be the next). Dr.

1. A welcome attempt to displace the name "mongol" is made by three correspondents (G. Allen et al. *Lancet*, 1961, i, 755; C. W. Dunn, *ibid.* p. 1116; A. Caratzali, *ibid.* Though we would accept that "Down's syndrome" is better than mongolism, we continue to believe that "21-trisomy" is an adequate and accurate term.
2. Lennox, B. *Lancet*, 1961, i, 1046.
3. Jacobs, P., Harnden, D. G., Buckton, K., Court Brown, W. M., King, M., MacBride, J. A., MacGregor, T. N., Maclean, N. *ibid.* p. 1183.
4. Hirschhorn, K., Decker, W. H., Cooper, H. L. *ibid.* 1960, ii, 319.
5. Black, C. E., Bishop, A., Caley, J. P. *ibid.* p. 1450.
6. Ferrier, P., Shepard, T., Garther, S., Burt, B. *ibid.* 1961, i, 1170.
7. Ford, C. E., Polani, P. E., Briggs, J. H., Bishop, P. M. F. *Nature, Lond.* 1959, **183**, 302.
8. Vaharu, T., Patton, R. G., Voorhess, M. L., Gardner, L. I. *Lancet*, 1961, i, 1351.
9. Fraccaro, M., Ikkos, D., Kaijser, K., Lindsten, J., Luft, R. *ibid.* 1960, ii, 114. (See also J. Lindsten, *ibid.* 1961, i, 1228.)
10. Black, C. E., Gordon, R. R., Bishop, A. *ibid.* 1961, i, 947.
11. Chu, E. H. R., Warkany, J., Rosenstein, R. B. *ibid.* p. 786.
12. Bloise, W., de Assis, L. M., Bottura, C., Ferrari, I. *ibid.* 1960, ii, 1059.
13. Oikawa, K., Blizzard, R. M. *New Engl. J. Med.* 1961, **264**, 1009.
14. Ferguson-Smith, M. A., Johnstone, A. W., Handmaker, S. D. *Lancet*, 1960, ii, 184.
15. Carr, D. H., Barr, M. L., Plunkett, E. R., Grumbach, M. M., Morishima, A., Chu, E. H. Y. *J. clin. Endocrin.* 1961, **21**, 491.
16. Fraccaro, M., Lindsten, J. *Lancet*, 1960, ii, 1303.
17. Carr, D. H., Barr, M. L., Plunkett, E. R. *Canad. med. Ass. J.* 1961, **84**, 873.
18. Anders, G., Prader, A., Hauschteck, E., Schärer, K., Siebenmann, R. E., Heller, R. *Helv. pædiat. Acta*, 1960, **15**, 515.
19. Patau, K., Smith, D. W., Therman, E., Inhorn, S. L., Wagner, H. P. *Lancet*, 1960, i, 790.

CRAWFURD's case-report on p. 22 today, added to earlier records from Birmingham,[20] Wisconsin,[21] and (less certainly) Nijmegen,[22] confirms the existence of a recognisable syndrome for no. 17. All the patients were mentally defective infants who have died, or been likely to die, within a few months of birth. The chief stigmata are a small deformed mandible, low-set malformed ears, cranial deformities, flexion deformity of the fingers, and a short big toe, with deficient falx cerebri and congenital heart lesions. Some of these are common to a good many cases of severe chromosomal anomaly, but the total picture seems characteristic enough. Only an experienced clinician who has seen several cases is really in a position to judge, but the picture is probably as distinctive as that of trisomy-21. If acceptance of a syndrome can be said to be assured when variant forms begin to be described, CRAWFURD's case marks that interesting stage; for the extra chromosome in this case is believed to be partly deleted.

A nice point arises over the identification of the trisomic chromosome. EDWARDS et al.[20] called it no. 17, and SMITH et al.[21] and VAN WIJCK [22] called it no. 18; CRAWFURD is discreetly non-committal. If this is a genuine syndrome, it is beyond all genetic credibility that different chromosomes could be involved. Not many people really believe that 17 and 18 can be distinguished from each other, and the argument is at present sterile. Very much the same applies to chromosomes 21 and 22, especially since it has been shown that they cannot be clearly distinguished by their satellites. There is, however, a gentleman's agreement that the one concerned in mongolism shall be called 21: indeed, it has been argued with force that the best definition of 21 is its ability to produce that disease. Might we not accept the same for the new syndrome? EDWARDS et al. have priority, and called it trisomy-17: would it not be sufficient to accept this name, and (topsy-turvy as it may seem) to agree that, whatever refinements of identification may appear in future, the chromosome which produces it may be called no. 17? It would save a deal of argument.

Parkinsonism

DISCUSSION of the physiology of the basal nuclei, which not so long ago was almost metaphysical, has now become more solidly based. This change has been much aided by the trend towards considering the function of any one part of the brain in relation to the brain as a whole. Thus DENNY-BROWN,[23] in an analysis of the functions of the basal nuclei, spoke of reflex circuits, of balance between conflicting automatisms, and of release of another set of cortical reactions after destruction of one which would normally inhibit it from time to time. In so far as he allocates function to the different nuclei, DENNY-BROWN suggests that the putamen is necessary for elaboration of contactual exploratory and avoiding responses and of labyrinthine responses into optic reactions. Dysfunction of this part releases coarse reflexes, which produce athetosis with alternating postures outlasting the stimulus; these may affect limbs, trunk, or eye movements. Severe destruction releases dystonic patterns reminiscent of lower reflexes of labryinthine and contact-righting responses, with adoption of the " decorticate " posture when the patient is held free of support to the trunk. The globus pallidus, says DENNY-BROWN, is necessary for righting reflexes. Mild lesions result in parkinsonian tremor, and severe ones in akinetic mutism with general flexion of the proximal joints, pronation of the forearms, and extension of the fingers. Certain thalamic labyrinthine reactions lead to rigidity; and overaction of thalamic reflex circuits play a part in tremor, which he regards as a rhythmic alternation between conflicting reflexes deprived of their higher control, modification, and inhibition. Destruction of the subthalamic nucleus leads to hemiballismus, and of the substantia nigra to loss of the power to chew and swallow. The caudate nucleus, according to DENNY-BROWN, is concerned with suppression of certain groups of cortical reactions while another is active, and he suggests that the reactions concerned may vary in different parts of this extensive nucleus. Mild lesions of the caudate nucleus and of the frontal cortex lead to chorea; and in monkeys destruction of the head of the nucleus produces " hyperactivity "—a form of augmented forward progression—and releases visually determined automatic behaviour of investigation, challenge, and avoidance.

Such an analysis, although tentative, is invaluable. Certainly reflexes which involve a particular nucleus after other parts of the brain have been destroyed do not necessarily represent the function that nucleus in the intact brain. Furthermore " mild " lesions may disturb function not only by " releasing " coarser reflexes [24]: they may actually produce an alternating balance between opposing reflexes. The caudate nucleus has commonly been supposed to be suppressive; but there seems no sound reason why this should be so except in so far as any active cerebral process must suppress other functions: visual investigative automatisms, for example, are released by temporal-lobe lesions. From the results of stimulation and destruction TURNER [25] suggested that the head of the caudate nucleus may be necessary for reflex movements of recoil and retraction. If any site is pre-eminent in holding a " balance " between different cerebral functions it is likely to be the diffuse projection systems in the thalamus and brain-stem. By this token the cerebrum is a series of parallel goal-seeking neural circuits competing for the central neuronal pool in the diencephalon.

Against this physiological background parkinsonism can be better understood.

DENNY-BROWN found that in paralysis agitans pathological changes were multiple but mild, with loss of cells in the globus pallidus, striatum, substantia nigra, and locus cœruleus of the pontine tegmentum, and with

20. Edwards, J. H., Harnden, D. G., Cameron, A. H., Crosse, V. H., Wolff, O. H. *ibid.* p. 787.
21. Smith, D. W., Patan, K., Therman, E., Inhorn, S. L. *J. Pediat.* 1960, **57**, 338.
22. van Wijck, J. A. M., Stolte, L. A. M., Van Kessel, H. I. A. M., Tijdink, G. A. J. *Lancet*, 1961, i, 887.
23. Denny-Brown, D. *ibid.* 1960, ii, 1099, 1155.
24. *Lancet*, 1959, i, 1028.
25. Turner, E. *J. Neurol. Psychiat.* 1957, **20**, 216.

paravascular degeneration principally in the globus pallidus, and pallor in the ansa lenticularis. In arteriosclerotic disease a lacunar state with multiple small infarcts in the putamen was associated with severe rigidity and a fixed " hemiplegic " posture. The more lateral the lesions in the globus pallidus, the more prominent was dystonia. In postencephalitic parkinsonism lesions were even more widespread, and clinically there were disturbances of posture reminiscent of more elaborate automatisms—for example grotesque postures of limbs, violent and extensive tremor, and compulsions such as oculogyric crises.

COOPER,[26] in a study of 5000 patients with parkinsonism of whom 1000 were submitted to operation, found, besides the triad of tremor, rigidity, and abnormal gait, bradykinesia which might be secondary to rigidity when the ability to move rapidly on occasion was retained, or primary when there was muscular weakness.[27] Mask-like features, oculogyric crises, spontaneous laughing or crying, overbreathing, hyperthermia and excessive sweating, dysphagia, and dysphonia were also common. Mental abnormalities included schizophrenia, anxiety fears, passivity, dependency, rigid personality, depression, and over-reactivity to stress, and in some instances presenile or senile dementia. Symptoms were frequently first noted, and tended to be exacerbated, after periods of great emotional stress. After trying occlusion of the anterior choroidal artery and pallidectomy, COOPER concluded that the most effective surgical measure was destruction of the ventrolateral nucleus of the thalamus. The surgical lesion was thought to include the reticular nucleus of the thalamus, zona incerta, and afferent fibres to the thalamus from the globus pallidus, cerebellum, red nucleus, vestibular nucleus, and cerebral cortex. With this procedure COOPER has successful results in more than 85% of carefully selected patients; the mortality-rate was 2%. Tremor particularly was more uniformly relieved than with pallidectomy. Complications included motor or sensory impairment in 6%, and this persisted in 3%. Somnolence or confusion occurred in 8%, but was temporary (permanent confusion and impairment of memory is known to ensue occasionally). Dysphonia, aphasia, or mutism was noted in 10%, and was also usually temporary. Hyperpyrexia, hypokinesia, dysphagia, pneumonia, and urinary retention developed in postencephalitic cases, but these were transient. Other forms of dyskinesia, varying from choreic movements to hemiballismus, occurred postoperatively in 3·6% of cases; rarely this, too, persists.

In the light of extensive surgical experience it is hard to believe that destruction of the medial part of the globus pallidus alone can have the severe consequences attributed to it—in particular it does not produce akinetic mutism, which certainly results from destruction of the anterior hypothalamus. Likewise destruction of the ventrolateral nucleus of the thalamus seems to be free of dire sequelæ. As we have already suggested,[24] absence of a coordinating system or " smoothing circuit " can be less of a handicap than a faulty one.

26. Cooper, I. S. *Ann. intern. Med.* 1960, **52**, 483.
27. Schwab, R. S., England, A. C. *Neurology*, 1959, **9**, 65.

Tuberculous Refugees

LAST year in a survey of Europe's refugees [1] we drew attention to the special problems of the tuberculous in regard to immigration. One difficulty in arriving at a fair assessment of the position has been the lack of accurate estimates of the number of tuberculous refugees wishing to emigrate and the fate of those who do. The regulations about tuberculous immigrants have in the past been remarkably strict; and some believe that they are out of date, now that the treatment of the disease has become so much easier and more effective. It has even been suggested that the regulations " sometimes appear to be used, not to protect the population of the receiving country, for which they were devised, but to select the few from the many ".[2]

It is still difficult to find out the total number of tuberculous refugees; but there is now more information about what has happened to those who have been accepted for immigration under special schemes or treated in the country that first received them. SCHOU,[3] of the Intergovernmental Committee for European Immigration, has reported a follow-up of Hungarian refugees who entered Austria in 1956. Of 16,226 X-rayed during the next two years, 385 were found to have " possibly active " pulmonary tuberculosis and 388 a " post-tuberculous " state. A survey of these 773 individuals was carried out in November, 1960, when 420 had left Austria and 353 remained. Of those with possibly active disease 63% had left, compared with only 45% of those with a post-tuberculous state. This finding illustrates how the post-tuberculous fall between two stools. They are rejected for mass emigration because their disease is not regarded as definitely arrested, and they are rejected for special schemes because their disease is not sufficiently active. Of the 353 who were still in Austria, 301 had already been integrated into the community, and only 52 still desired to emigrate. The majority of the patients with active disease who had already emigrated had gone under special schemes to Denmark, Norway, or Sweden. Of 50 who went to Denmark in 1957, 49 were in hospital for less than a year and 48 were at work and self-supporting within eighteen months of arriving in the country.

Between 1950 and 1959 Sweden accepted 1011 tuberculous refugees.[4] By January, 1960, only 32 were still in hospital, and 26 of these had arrived in the preceding two years. 557 were admitted between 1950 and 1956, with pulmonary tuberculosis which was far advanced in 101 and active in 422. More than 40% of those taken into hospital were discharged within six months and 70% within a year. Of the 438 about whom information is available, more than a quarter were at work within six months of arrival and more than half within a year. Only 1 in 10 remained unfit for work, and in a quarter of these the unfitness was due to diseases other than tuberculosis.

The refugees admitted to these Scandinavian countries were deliberately selected as patients requiring treat-

1. *Lancet*, 1960, i, 481.
2. *Tubercle, Lond.* 1960, **41**, 380.
3. Schou, C. *ibid.* 1961, **42**, 227.
4. Bruce, T. *Svenska NatFören. Tuberk. Kvart.* 1960, **55**, 36.

ment, whom at that time no other country but Switzerland would accept. The facts about their progress certainly do not indicate that they would have been either a grave financial burden or a noticeable public-health risk if they had been admitted to the countries that barred their frontiers against them.

World Refugee Year brought some relaxation of the regulations, and Great Britain and other countries agreed to accept refugees with active tuberculosis. Great Britain was prepared to accept 200 handicapped refugees, and 20 with tuberculosis were accepted; but only 5 of these had disease so severe as to require hospital treatment. In March, 1960, it was stated that persons with curable tuberculosis would be admitted. But the criteria of curability were not stated, nor is it known what authority on tuberculosis decided who was curable or who incurable.

Canada, one of the countries with the most strict regulations for excluding the tuberculous, has, in fact, accepted over 700 persons with active disease. As part of its contribution to World Refugee Year, a special fund was set up to take tuberculous patients and their families to Canada. In December, 1959, and January, 1960, a hundred families were admitted, and these were integrated into the community so rapidly that a second group of 39 families was admitted in June. The Canadian Secretary of State for Foreign Affairs declared last December, that the period of treatment and integration of these tuberculous families had proved to be shorter than was originally estimated and that a third group was to be admitted. Of the first 100 tuberculous refugees only 38 had moderately or far advanced disease. Three months after arrival in Canada 58 patients had been discharged from hospital, 3 were awaiting discharge, and only 7 still had tubercle bacilli in the sputum.

The picture that emerges from these few investigations of the after-history of tuberculous refugees admitted as immigrants supports the view that there "appear to be no medical grounds for excluding any refugee with tuberculosis, curable or incurable, from entering Great Britain".[2] In World Refugee Year the antiquated regulations were relaxed. What was begun by compassion might now be extended through reason.

Annotations

GROUPING LONDON'S POSTGRADUATE TEACHING HOSPITALS

THIS week the Minister of Health made his expected [1] statement on postgraduate teaching hospitals in London (see p. 57). The main feature of his plan is the transfer to a site near the Royal Marsden and Brompton Hospitals, in Fulham Road, of three urological hospitals (St. Peter's, St. Paul's, and St. Philip's), of St. John's Hospital for Diseases of the Skin, and of St. Mark's Hospital. Secondly, the group of hospitals in the Holborn area is to be increased by the addition, on the present site of the Royal Free Hospital, of a unified Moorfields Eye Hospital. Hammersmith Hospital, the Maudsley and Bethlem Hospitals, and Queen Charlotte's Hospital (with the Chelsea Hospital for Women to be rebuilt nearby) are unaffected.

This plan, by which the main localities of postgraduate teaching will be reduced to five or six, has much to commend it. But important questions remain to be answered —including the timing of the whole operation, the extent to which the grouped hospitals are to share services, and how these specialised hospitals are to be assured of their essential links with general hospitals. One clause in the Minister's statement must be rated as disappointing. This is that "Provision will be made for the eventual inclusion [on a site in Fulham Road] of the National Heart Hospital and the Institute of Cardiology". So far as it goes, this suggests that the Ministry is willing for the transfer to take place. But the Ministry is not the only body concerned; and elsewhere there may be reluctance to see the National Heart Hospital moved—cramped, inadequate, and isolated though it is—on the ground that much thought and work have gone into its development. Yet surely the chance should be seized to correlate the study and treatment of cardiovascular and of respiratory diseases. Such integration could be one of the largest gains from development of the Fulham Road group of hospitals.

1. See *Lancet*, 1961, i, 1269.

FAMILIAL MEDITERRANEAN FEVER

THE earliest reports of familial Mediterranean fever related to Jewish patients in the United States [1]; but the full range of the clinical features of this remarkable condition were perhaps first appreciated in France through observations on immigrants from North Africa.[2] The illness is almost confined to peoples originating from the southern and eastern shores of the Mediterranean; and those who write on it tend to have such pleasingly unfamiliar names as Mamou [2] and Benhamou [3] (North Africa), Semerdjian and Sahyoun [4] (Lebanon), and Artunbal and Seyahi [5] (Turkey).

The disorder is characterised by recurrent attacks of pain in the abdomen, chest, or joints, with fever, sometimes an erysipelas-like rash, and quite often progressive renal disease. The condition was early recognised as running in families. Four physicians in Tel-Aviv [6] have completed a genetic analysis based on 262 index patients, drawn from all the public hospitals in Israel, of whom 232 were available for the family study. This large series shows clearly that the great majority of cases are due to the homozygous state of a recessive gene. There was a raised prevalence (over 20%) of parental consanguinity; and about 1 in 4 of the sibs (but few relatives of other degree) were affected. In a few families a dominant gene was apparently responsible. One such is the Armenian family reported by Reimann et al.[4] from the Lebanon. Another is the family reported from Switzerland by Bickel and Lesserne [7]; this, too, was an Armenian family from the Lebanon, and may have been a related kindred.

Israel, where most of the inhabitants are immigrants, is well suited to the study of variations of gene frequency in different human populations. The largest group of immigrants—over half the whole—are Ashkenazi Jews, but only 6 of the patients belonged to this group. In

1. Siegal, S. *Ann. intern. Med.* 1945, **23**, 1.
2. Mamou, H., Cattan, R. *Sem. Hôp. Paris*, 1952, **28**, 1062.
3. Benhamou, E., Albou, A., Sayag, P. *Algérie méd.* 1955, **59**, 809.
4. Reimann, H. A., Moadie, J., Semerdjian, S., Sahyoun, P. F. *J. Amer. med. Ass.* 1954, **154**, 1254.
5. Artunbal, S., Seyahi, V. *Bull. Soc. turq. Méd.* 1955, **21**, 282.
6. Sohar, E., Prass, M., Heller, J., Heller, H. *Arch. intern. Med.* 1961, **107**, 529.
7. Bickel, C., Lasserne, R. *Schweiz. med. Wschr.* 1957, **87**, 5.

contrast, 250 patients belonged to the smaller groups of Eastern Mediterranean and North African Sephardi Jews and Iraqi Jews. No cases were seen in Yemenite or Persian Jews; but a few of the patients belonged to the Armenian community of Lebanon and Israel, and a few were Arabs from Lebanon and Israel. The observed frequency of the homozygotes in the Sephardi Jews is of the order of 1 in 2500, and so the gene frequency in these populations must be of the order of 1 in 50.

Any recessively determined disorder is prima facie likely to be due to an enzyme defect, and the Tel-Aviv workers note that amyloidosis is a constant and early feature of the disease.[8] This, they believe, is responsible for the nephrotic syndrome which complicates the disease. The duration and severity of the recurrent attacks are apparently unrelated to the renal lesions; hence the clinical attacks and the amyloid disease may be parallel manifestations of the underlying biochemical disorder. New knowledge of amyloid disease suggests that the biochemical abnormality should be sought in the protein products of plasma cells.[9]

MEDICINE AND SOCIAL MEDICINE IN DEVELOPING COUNTRIES

HUMAN anatomy and human physiology have a universal application throughout the species; and thus medicine, which is based on them, should be universally valid also. Morbid processes and their correction will be the same everywhere. Nevertheless difficulties arise when attempts are made to bring modern medicine to people who do not understand its scope and limitations and may never have conceived that anyone could ask the sort of questions that doctors expect patients to answer. Some of the problems that are encountered and some ways in which they may be tackled are set forth in a report to the World Health Organisation from the department of social and preventive medicine at the University of Lucknow, in the State of Uttar Pradesh, India, by Prof. A. Leslie Banks as visiting professor and Prof. B. G. Prasad as national professor—i.e., the permanent head of this department.

India has, of course, a long and vital tradition in the practice of modern medicine on the Western model, and also an ancient rural culture to which 85% of the people belong. Fortunately the city-bred are still close enough to this to understand and value it, while medical care can be superimposed without destroying the culture itself. Much of the report is familiar reading: the size of the problems to solve, shortages of staff and accommodation, pitifully inadequate salaries, and huge classes—all are none the less real for being familiar. This department is first defining the problems it faces, and its members are reporting on vital statistics and on morbidity levels, undertaking infestation surveys, and trying to improve among the rural population such fundamental things as water-supplies and latrines, having such essential people as engineers, statisticians, and labourers on the staff. Practical work and practical teaching of this kind are carried out at a village health centre run by the department. Postgraduate students are accepted for an M.D. degree, while undergraduate teaching is given as far down as the first year. In later years practical work is given along the lines introduced by, for example, the Australian missionary, Dr. Edna Gault, at Vellore in South India.

8. Heller, H., Sohar, E., Gafni, J., Heller, J. *Arch. intern. Med.* 1961, **107**, 539.
9. *Lancet*, June 3, 1961, p. 1215.

All this is excellent and could be an example to many medical centres in many countries. When the planned preliminary labours are completed, many more similar studies could be suggested—e.g., on the incidence of poliomyelitis and of rheumatic fever (which is certainly quite common in parts of India). But the report also raises a larger issue—namely, how far should a department of social medicine extend? No doubt too much restriction should be avoided at first, and a modus vivendi with other departments should be allowed to emerge. But, to the outsider, it seems doubtful whether such a department should permanently have responsibility, for instance, for giving separate lectures on elementary psychology to junior students.

In an official report intended for wide circulation many matters must be omitted or acquiesced in. Thus it would be interesting to know the conditions under which "the Ayurvedic College at Varanasi is to be upgraded to the full five-year M.B., B.S. course"; for Ayurveda is not "orthodox" medicine—not at all.[1] Professor Prasad has already stated[2] that at Lucknow medical academic appointments are obtained in open competition, which is by no means the case throughout India. Nothing is said in the report about selection of postgraduate students, but presumably they are nominated by the medical services of the various States. The report assumes that medicine can best be taken to the poor villager by State-organised rural health centres, such as the one run by the department; but it does not discuss their organisation or consider how doctors can be persuaded to devote their lives to serving in them—perhaps the most urgent difficulty of medicine in India today, and not in India only. There is also the obstacle of traditional customs that defy hygiene; for both detailed knowledge and great tact are required if these are to be modified without outraging sensibilities. Even the great Gandhi, when discussing sanitation among the poor, wrote: "The floors were beautifully smeared with cow dung. . . . There was no fear of an outbreak in those quarters."[3] Such customs are by no means confined to India.

In some ways the report is bold. Thus the average age at marriage for females in the villages surveyed is stated after investigation to be 11·9 years, and for males 13·2—far below the legal minimum of 16 for females and 18 for males. This ancient wrong is evidently far from being righted. Once more Gandhi inveighed against it, having himself been married at 13.

The department from which this survey comes will obviously get things done if anyone can. The needs of its community have led to its concentrating on general problems of public health; and probably this is the way in which it can be most immediately useful. But, looking at the situation from a long way off, one wonders whether a department of social and preventive medicine in India would not, in the long run, be even better employed in doing things that nobody else can do at all—concentrating on researches into how the local social customs and organisation could be used to spread enlightened medicine without themselves suffering. "Social medicine" has always been open to different interpretations; but the so-called developing countries probably need it in its stricter form as much as they need the larger kinds of public health. So indeed may the countries which already enjoy the mixed benefits of being fully industrialised.

1. Shastri, M. K. *J. Ind. med. Prof.* 1955, **2**, 616.
2. Prasad, B. G. *Lancet*, 1960, i, 494.
3. Gandhi, M. K. An Autobiography (translated by M. Desai). Ahmedebad, 1927.

LUNG PURPURA WITH NEPHRITIS

THE clinical picture of acute glomerulonephritis varies little, and involvement of organs other than the kidney is rarely significant. In the Henoch-Schönlein syndrome, however, nephritis may be associated with purpura affecting skin, joints, and intestine; and the disease is characterised histologically by capillaritis at affected sites. Many organs, including the kidney, may be affected in polyarteritis nodosa, which is recognised pathologically by widespread arteritis predominantly involving smaller arteries and arterioles. Renal damage in polyarteritis nodosa may take the form of either multiple infarcts or diffuse parenchymal change, due respectively to involvement of the larger or smaller renal arteries.[1 2] In the latter form of the disease, the clinical presentation of proteinuria, hæmaturia, and azotæmia without gross hypertension may be indistinguishable from that of severe acute glomerulonephritis; but diagnosis may be suspected if there is simultaneous involvement of other tissues—for example skin, joints, and lungs—and the suspicion is strengthened if fibrinoid arterial or arteriolar necrosis is found at affected sites. Since necrotising arteritis in the kidney has been described in the rapidly progressive form of acute glomerulonephritis,[3] such changes must be demonstrated also in other organs before polyarteritis nodosa is firmly diagnosed.

Rusby and Wilson [4] have described a severe form of nephritis in five young males in whom frank hæmoptysis was an early and prominent clinical feature. The association of pulmonary hæmorrhage with nephritis has been previously reported; but evidence of polyarteritis nodosa has been demonstrated in more than half of these patients. For example, Goodpasture [5] reported postmortem findings in an 18-year-old male in whom repeated hæmoptysis had been a striking feature of an apparent influenzal illness. The kidneys showed a proliferative glomerulonephritis of which there had been no indication in life apart from a trace of protein in the urine. Examination of the lungs revealed gross hæmorrhage with small areas of necrosis in alveolar walls; and, although no evidence of pulmonary or renal arteritis was found, microscopic study showed vascular lesions in both spleen and intestine—changes certainly suggestive of polyarteritis nodosa. In 1954 clinical and pathological details were published of a 24-year-old man in whom repeated hæmoptyses preceded severe nephritis with progressive renal failure.[6] At necropsy the finding of fibrinoid necrosis of afferent arterioles in the kidney, pulmonary arteritis with multiple infarcts, and acute arteritis affecting pelvic arteries enabled polyarteritis nodosa to be conclusively diagnosed.

Parkin et al.[7] recorded hæmoptysis as a prominent early feature in 7 patients with fatal nephritis. Postmortem examination of the kidneys showed proliferative glomerular changes with crescent formation and a few areas of fibrinoid necrosis within glomeruli, and in 1 case a necrotising renal arterial lesion was found. The lungs showed necrotising alveolitis with hæmorrhage; and, although a pulmonary arteritis was found in only 1 instance, in 4 there was fibrinoid necrosis of small arteries at other sites—for example, spleen, gallbladder, appendix, liver, and pancreas. On this evidence, it seems probable that polyarteritis nodosa was the underlying diagnosis in at least half of the 7 patients. Stanton and Tange [8] described 9 cases of pulmonary hæmorrhage and acute glomerulonephritis, and suggested that polyarteritis nodosa was the underlying cause in 3. In a case reported by Scadding [9] repeated hæmoptyses for nine months preceded proteinuria and moderate uræmia; renal failure led to his death two months later, and necropsy showed severe glomerulonephritis. Lung biopsy had previously shown interstitial hæmorrhage, but there was no evidence of arteritis either in the kidneys or elsewhere. Lexow and Sigstad [10] reported initial lung purpura with glomerulonephritis in a man aged 30 in whom hæmoptysis preceded recognition of renal involvement by four weeks. He died from uræmia within a few weeks, and at necropsy the kidneys showed glomerulonephritis without arterial or arteriolar necrosis. The pulmonary arterial walls were somewhat thickened, but there was no evidence of vascular necrosis.

Of the 5 cases described by Rusby and Wilson all were males aged 17–22; and 4 died from rapidly progressive renal failure three to twelve months after the onset, while the 5th was still alive after three years. Hæmoptysis was the first symptom in all patients, and the interval between this and recognition of renal involvement varied from five weeks to eight months. In no instance was there bacteriological evidence of pulmonary or other infection which might have been responsible for the development of acute glomerulonephritis. The early phase of the disease was marked by repeated hæmoptyses with inconstant and transient radiographic changes in the lungs. The phase of renal involvement was recognised by the discovery of proteinuria with or without red blood-cells and casts in the urine. Hypertension occurred in only 2 of the 5 patients. 1 presented a nephrotic picture before passing rapidly into renal failure, while the remaining 3 fatal cases progressed at an early stage to oliguric renal failure with uræmia. The surviving patient had no hypertension or azotæmia at any stage.

In this study, renal tissue was procured by needle biopsy as early as four weeks after the recognition of nephritis; biopsy was not undertaken in the case of the surviving patient. Postmortem examination of the 4 patients who died revealed diffuse or focal necrosis of glomerular tufts with or without crescent formation. Necrosis (fibrinoid in 2) affected afferent glomerular arterioles in 3, while in 1 of these there was also necrosis in the wall of an interlobular artery. On this evidence it is difficult, in at least 3 of the 5 cases, to substantiate any histological differentiation of the renal condition from the microscopic form of polyarteritis nodosa. Histological examination of the lungs, however, showed no pulmonary arteritis in the 3 cases in which a detailed report was given, the changes described being those of diffuse hæmorrhage. Reference to blood-vessels other than renal and pulmonary was made in only 1 instance, in which petechial hæmorrhages in the gut were described; but in this patient the blood-urea had reached 660 mg. per 100 ml. before death.

Rusby and Wilson comment on the remarkably consistent clinical pattern of disease in these 5 patients—all young men in whom hæmoptysis long preceded known evidence of renal involvement. Since no necrotising

1. Gruber, G. B. *Virchows Arch.* 1925, **258,** 441.
2. Davson, J., Ball, J., Platt, R. *Quart. J. Med.* 1948, **17,** 175.
3. Fishberg, A. M. *Arch. intern. Med.* 1927, **40,** 80.
4. Rusby, N. L., Wilson, C. *Quart. J. Med.* 1960, **29,** 501.
5. Goodpasture, W. E. *Amer. J. med. Sci.* 1919, **158,** 863.
6. Hammersmith Hospital, Clinico-pathological Conference no. 21. *Post Grad. med. J.* 1954, **30,** 35.
7. Parkin, T. W., Rusted, I. E., Burchell, H. B., Edwards, J. E. *Amer. J. Med.* 1955, **18,** 220.
8. Stanton, M. C., Tange, J. D. *Aust. Ann. Med.* 1958, **7,** 132.
9. Scadding, J. G. *Proc. R. Soc. Med.* 1958, **51,** 649.
10. Lexow, P., Sigstad, H. *Acta med. scand.* 1960, **168,** 405.

alveolar changes were found in the lungs, Rusby and Wilson draw an analogy between the lung purpura of this condition and that of idiopathic pulmonary hæmosiderosis. They suggest that differentiation of the condition from polyarteritis nodosa is justified clinically by the absence of systemic features such as fever, eosinophilia, increased erythrocyte-sedimentation rate, leucocytosis, and polyneuritis, and pathologically by the absence of arteritis affecting larger vessels and by the relative scarcity of necrotic changes in the smaller vessels. In at least 3 of the 5 cases there was necrosis of afferent glomerular arterioles (with necrosis of an interlobular artery in 1), and clear histological differentiation of the renal lesion from the microscopic form of polyarteritis nodosa is impossible. For practical purposes, however, it may be valuable to recognise a clinical syndrome of lung purpura with nephritis, the prognosis of which is very much less favourable than that of uncomplicated acute glomerulonephritis for the same age-group. Further studies are required to establish the nature of the underlying histological abnormality in the kidneys and lungs, and to determine whether there is a more widespread vascular abnormality identical with or similar to that in polyarteritis nodosa.

GANG ANALYSIS

FOR many years psychological explanations of crime have been pre-eminent, but of late the importance of its social setting has been reasserted, and in their study of delinquent gangs in the U.S.A. Cloward and Ohlin [1] suggest that criminality is essentially a property of the social systems in which the criminal lives rather than of personal psychological maladjustment. They believe that the high crime-rates in certain areas are created by stress and strain within the structure of society because of vital inequalities. People in these deteriorated social districts feel that they can never achieve their full economic and status aspirations by legitimate means. Unlimited personal achievement, especially in terms of economic rewards, is the incentive dangled before the nose of every American citizen, but in a freely competitive society it is impossible for everyone to realise their aspirations. For every success there must be a number of failures. Those who fail are acutely frustrated and have to face serious social disadvantages. One way of reacting to this defeat is to join the criminals in their battle of wits against respectable society.

Cloward and Ohlin divide the members of this slum subculture into three groups:

Criminal groups, who compensate for failure to succeed in the normal society by creating their own underworld in which they can gain both financial rewards and prestige through illegitimate skills. These groups have their own internal organisation and controls, and what may be called an apprenticeship system which offers promotion to a select number of juvenile delinquents.

Conflict groups, usually composed of immigrants and newcomers, who resent the indifference of the respectable world and seek to attract attention by exhibitions of violence. These gangs are typically " boppers " and swaggerers who attain status by aggressive behaviour which transforms social alienation into attention by the exercise of brute force. Their members are usually youths and teenagers.

Retreatist echelons of the hipster variety, who are convinced of their own inadequacy. They no longer strive for acceptance by respectable society, but are content to withdraw into a twilight zone in pursuit of the kick provided by alcohol, marijuana, drug addiction, unlicensed sexuality, and both hot and cool jazz.

Cloward and Ohlin admit that so far only fragmentary and impressionistic evidence supports their analysis; and, as in much recent American sociological writing, the gap between social theory and empirical research is wide. For this country their theory may have less urgent implications. Our society has somewhat different goals and values, and drug-addiction and inter-gang warfare are fortunately still rare. Though we should be wise not to ignore the offender's social setting we must continue to seek other reasons for his misbehaviour, not excluding personal psychological dysfunction.

1. Delinquency and Opportunity: a Theory of Delinquent Gangs. By RICHARD A. CLOWARD and LLOYD E. OHLIN, New York School of Social Work, Columbia University. London: Routledge and Kegan Paul. 1961. Pp. 220. 25s.

A LUSTY MAJORITY

ON June 29, the 21st anniversary of the day when Lord Nuffield signed the deed which created the Nuffield Provincial Hospitals Trust, its fifth report [1] was published. It is a record of things done and things begun in 1958–61 with the help of grants of over £1,050,000. In choosing subjects for study and investigation the Trust has been mindful that the National Health Service is soon to have a " strong infusion of capital ". Scientific examination of beliefs and hypotheses is a prudent preparation for expansion, and studies of present working will help to assess future needs. No doubt the Government itself will initiate useful surveys, but even so the Trust believes that there will be room for the " lustiness of independent bodies ".

In these last years the Trust has wisely given special support to " operational research " such as the organisation and planning of central sterile supply departments, X-ray diagnostic departments, and the engineering services which provide hospitals with heating, ventilation, and water. The Trust recognises that the hospitals, being only part of the National Health Service, cannot be studied in isolation. The domiciliary and personal health services are important not only in their own right but also in their influence on the hospital service. An important point of contact between the different parts of the health service is hospital casualty and outpatient departments, and this has led the Trust to sponsor outpatient surveys in Manchester and Edinburgh, and a study of the casualty services was published last year.[2] Another point of contact is the care of the mentally ill, and the Trust's interest in this continues. New projects going forward with its backing include community mental health centres at Plymouth and Swansea, a domestic reablement unit at a Warwickshire hospital, and studies and surveys of the prevalence of mental illness in different parts of the country. Birmingham's ambitious and imaginative plans for a balanced hospital community [3] have also received a substantial grant.

In the introduction to the report there is an acknowledgment of how much the Trust owes to the liveliness of mind and freshness of approach of the late Sir Ernest Rock Carling. In his memory an annual fellowship is to be created. The fellow will be asked to write a monograph on one of Sir Ernest's many interests and to give a lecture at a medical teaching centre which will crystallise " contemporary thinking . . . and provide fresh base-lines for future speculation and action ".

1. The Nuffield Provincial Hospitals Trust: a record of the progress of schemes and descriptions of new projects, 1958–1961. Issued by the Trust, Nuffield Lodge, Regent's Park, London, N.W.1.
2. See *Lancet*, 1960, ii, 689.
3. See *ibid.* June 3, 1961, p. 1212.

Teaching of Everyday Psychiatry *

TEACHING PSYCHIATRY TO UNDERGRADUATES

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"We are anxious that the time spent by students on the psychiatric firm should be as useful as we can make it. This questionnaire is intended to keep us in touch with your needs, and it is hoped that you will answer the questions as fully and as constructively as possible. Please do not sign the form. After completion it should be sealed in the attached envelope and handed to one of the hall porters in the school or hospital for delivery."

FROM 1956 a questionnaire with this request as a heading was issued to every student at Westminster Hospital at the end of his work with the psychiatric firm. In three years about 150 copies were issued, and 110 were returned completed—i.e., about 73%. It seems opportune that the results should be published now, not only because of a world-wide concern about the teaching of psychiatry, but also because of a highly interesting report by the British Medical Students' Association (1959).

We are aware of the defects that may be attached to the views of the medical student. Unless he comes from a medical family—and fewer now do—he will have no real concept of the size or the difficulty of the psychiatric problems that will face him in practice. According to temperament he may exaggerate or underrate these; or, of course, he may assess them fairly accurately. Secondly, because he is still maturing and his *Weltanschauung* is a little unsettled, his contact with psychiatric patients may arouse anxieties of a more personal kind than those he experiences when he sees cancer in the middle-aged. If he is religious he may have difficulties in distinguishing Mind, of which brain is the organ, and Spirit. He cannot be blamed if this is so, for some of his seniors have similar difficulties. Finally, because he has to be realistic, he may be influenced by the fact that there will be no compulsory question on psychiatry in his final examination, and that if there is an optional question it will be marked by a general physician.

Despite these defects in his testimony, we believe the student qua consumer is entitled to be heard, especially as there is no other body that can claim to be free from stain. Even psychiatrists, we regretfully admit, might be thought by some to attach too much importance to the subject. Colleagues in other specialties, we readily agree, are certain to attach too little. General practitioners are perhaps the least suspect of all, and for that reason we shall draw attention to the report prepared by the working party of the College of General Practitioners (1958) which in relevant essentials agrees with the views of the students themselves.

PATTERN OF TEACHING

If the questionnaire and the replies are to be understood, a brief account must be given of the general pattern of teaching prevailing at the time.

Students were allocated to the psychiatric firm, and to two other firms, for a period of three months. During that time they attended one diagnostic clinic weekly, taken by one of us for a period of about $1^1/_2$ hours. As many others have testified, patients are seldom put out by the presence of students unless they have obviously embarrassing problems such as impotence, in which case they are seen alone later in the morning, or attend a diagnostic clinic when students are not present. Once weekly a case-demonstration is held, at which a student presents an inpatient whom he has written up fully without access to the case-notes. On yet another half day the students are taken by the chief assistant or senior registrar, and the form of the session varies a good deal. Films and tape recordings are used, demonstrations of psychological testing are given, physical treatments are shown, and four visits are made to a mental hospital. Every student goes once, though not necessarily during this period, to a hospital for the mentally defective. Four lectures are given in the introductory course in the first clinical year, eight formal lectures in the second year, and a further four in the final year. Instruction in child psychiatry is given once weekly by one of us in a diagnostic clinic at the children's hospital while the students are on the pædiatric firm.

In making this report we do not suggest that the pattern of teaching is either ideal or what we ourselves would wish it to be. In particular we believe that students will only learn psychiatry if they have time and opportunity to work quietly and privately with inpatients, following the evolution of the illness under treatment in exactly the same way as with somatic disease. For part of the period under review, students were over three times as numerous as the patients available. Towards the end of the period a reduction in the number of students and an increase in the number of beds altered the picture; so the pattern has not been static. This creates some difficulties in evaluating results, but we do not feel that they obscure the essential principles. Our desire is to report the reaction of students to what we believe to be fairly average facilities—not as good as those offered by some hospitals, but a good deal better than others.

THE QUESTIONNAIRE

Objective scoring has been difficult in some instances. Some students did not answer every question, and others answered in a way that was impossible to evaluate—e.g., the one who wrote: "If I may avoid a direct answer to the question . . ." (He did!) Another, when asked, "What teaching method was most useful?" said that "each complements the other"! We have not suppressed any criticism of the pattern of teaching except where it was facetious and devoid of useful content. This was very seldom: indeed, we have been surprised by the low incidence of facetious replies, and can only think that time has distorted our memories of our own undergraduate days. Where, occasionally, an adverse criticism of a colleague in another branch has crept in, we have suppressed it.

The following are our questions and an analysis of the answers.

1. *What teaching method did you find most helpful—attendance in outpatients, history-taking under supervision, tutorials, case demonstrations, lectures, or the reading of textbooks?*

Case-demonstrations	71	History-taking	11
Outpatients	29	Lectures	11
Tutorials	13	Textbooks	7

* A series of articles on the needs of students and practitioners, and how they may be met.

The reason why there are 142 responses from 110 students is that many do not state a definite preference but give two or even three alternatives. The figures demonstrate very clearly the students' preference for a case-demonstration with an inpatient, a full history having been taken, and the patient having been discussed for an hour. History-taking in outpatients, under the hurried conditions usually prevailing there, is comparatively low on the list. The small number of the believers in textbooks is in accord with experience in other specialties; for our colleagues tell us that a substantial proportion of students do not now buy even standard textbooks of medicine or surgery.

2. *Would you have liked more mental hospital visits to see psychotic patients (and if so, how many) or is the number adequate?*

More visits	50	Adequate	60

At present the number of visits is four and the average number suggested by those wanting more was six.

3. *Would you have liked more instruction in child psychiatry—e.g., what constitutes abnormal behaviour in a child, how parents should be advised, or the more technical forms of investigation and treatment?*

More instruction	76	Adequate	25

Teaching in child psychiatry is given during the students' period on the pædiatric firm, and some, at the time of filling in the questionnaire, had not been on this firm so that a number of opinions were reserved. Of the others, comment was suprisingly forceful. Thus:

" . . . surely it is a most important part of general practice."

" . . . it seems illogical to study pædiatric medicine and surgery whilst neglecting child psychiatry."

" . . . Personally I found the consideration of abnormal behaviour difficult owing to a deficient knowledge of the normal pattern of behaviour."

" Yes! I feel child psychiatry is sadly neglected . . . "

On the other hand: ". . . Personally I feel it is wrong to subject a child to psychiatric examination ".

4. *If you do not feel the instruction was well balanced, which of the following diagnostic categories should have received more attention? Please give only one: Neuroses, psychoses, organic and confusional states, psychopathy, mental deficiency, psychosomatic disorders.*

Well balanced	19	More psychopathy	16
More psychomatic medicine	31	More neuroses	7
More mental deficiency	20	More psychoses	6
		More organic states	6

The question about psychosomatic disorders was posed not because we particularly like the term but because we know that it is often used. To the student we believe the words suggest the integrating of psychological and somatic aspects of disease when both are prominent. These 31 students were almost certainly moved by feelings akin to the admiration expressed—rightly we think—by the British Medical Students' Association when referring to the " Sheffield Plan ".

Unconsciously we loaded this question against ourselves; and, although 86 students suggested that the course is not well balanced, they were kinder to us in question 10.

5. *Were you adequately instructed in psychiatric emergencies—e.g., certification, suicidal patients, the acutely disturbed? If not, what was lacking?*

Adequately instructed	42	Not so	63

Suicide, certification, and acute emergencies were all cited equally, but many stated that the legal aspects of psychiatry are well covered in textbooks. A feeling of inadequacy and a fear of being found wanting in a psychiatric emergency was expressed more than once:

" The layman's horror at having to deal with a drunk or a madman still persists. A G.P. lacking in confidence in this respect must lose a lot of face in front of relatives, the police, or any other spectators. The confidence of the knowledge of correct action would probably be very much to the advantage of the patient and my peace of mind."

6. *What aspects of psychiatry do you find most (a) boring, (b) interesting, and (c) difficult?*

The answers were very diffuse and do not lend themselves to computation. On the whole the legal aspects of psychiatry were thought the most boring, the psychoses the most interesting, and " borderline " cases the most difficult. The latter is reasonable enough, in that borderline, undiagnosed, and difficult tend to mean the same thing. It is a well-known phenomenon in case-conferences that students will go to great lengths to prove that a psychotic is not really psychotic but is neurotic or " borderline ". This, a defence against the personal anxieties of this age-group, improves towards the end of the period on the firm.

7. *From the point of view of examinations, what was lacking in the course?*

Most stated that they had no knowledge of what the examination questions were likely to be anyway, but that on the whole the course seemed to cover the facts. As a result of this very consistent reply we began to devote a tutorial or two to the question of examinations.

8. *Do you feel adequately instructed in the supportive methods of psychotherapy which can be employed by the general practitioner?*

Adequately instructed	41	Not so	67

More than one said that psychotherapy is merely a matter of commonsense, but others clearly regarded psychotherapy as a complicated technique requiring a specialised training outside the scope of the medical student. Some anxiety is shown by the student about the prospect of being faced with a patient requiring psychotherapy from him, and there is a tendency for such students to want to refer their cases for a " special opinion ". Thus:

" Isn't this mainly common sense? "

" No, but I doubt if it can be taught."

" I consider this a serious defect of the course as it seems essential to have a knowledge of psychotherapy in order to practice general medicine."

9. *Does Psychiatry attract you as a career?*

Attracted to psychiatry	27	Not so	79

This question aroused more comment than any other, and gives some—though not necessarily the best—indication of the average student's attitude to psychiatry. There were some clear negatives with exclamation marks, which did not suggest a compliment conveyed with subtlety. On the other hand, these were compensated by those who felt they lacked the necessary intelligence, patience, or personality! Very many said that they were interested to the extent that psychiatry could be applied in general practice. A fair selection of the comments made is as follows:

" No. I am happier with more practical work. Besides, I don't think I am the type that inspires confidences."

" Not in its more academic form. As an adjunct to general practice and with particular relevance to obstetric and the more long-term case (e.g., tuberculosis nursing). I am willing

to learn and put into practice any form of treatment which is to the advantage of the patient, especially in the form of encouragement (whether it is by the use of drugs or by carefully selected forms of occupation therapy &c.)."

" No. From the point of view of it being part of the armoury of the medical practitioner, however, it interests me intensely."

" Certainly not!"

" It occasionally does. In fact, I would give it more serious thought if I did not, at the moment, think that to be a psychiatrist one has to be a very well adjusted and integrated person or otherwise one tends to become environmentally influenced, especially if introverted to some extent, and end up as the layman says—the slightly mad psychiatrist."

" No. I dislike the idea of probing into people's minds and thoughts although I agree in some cases this is necessary."

" I do not think it does as a specialty but the importance and interest of it to the general practitioner certainly attracts me."

" I doubt my ability to be sufficiently objective in managing cases—but the firm has totally revolutionised my previous suspicious attitude to psychiatry."

" No. In so much as I feel that this is really a field for the first-rate mind, and not, if any progress is to made, suitable for an enthusiastic but average intellect."

10. *What further comment (of a constructive kind) would you like to make?*

Comments were made in just over 75% of the replies. As noted above, few were adverse and few were facetious. Many reiterated what had been said in answering the previous questions and others dealt with technical subjects such as the times of lectures and payment of fares when visiting mental hospitals.

Among the useful replies a desire to clerk inpatients and to " see the case through " from diagnostic clinic to ultimate discharge was outstanding. As, for reasons given, facilities for inpatients changed during the period under review, figures would not be meaningful.

After this came a desire to see psychotherapy being given. One reply was from a student who said he had never " realised actually that mental disease was not merely a theoretical and textbook disease ". He went on:

" One can hardly be blamed for the attitude that saw it as time wasted to read psychiatry. When, during the firm, the student was shocked into this reality that psychiatry is a practical problem, the time used in getting over the shock, coupled with the mental attitude built up over the previous two years of the clinical course that psychiatry is nothing to worry about, leave him with little time to get down to learning it. If it can be emphasised *early in our student career* that mental disease is real, students, I am certain, will show greater and more definite interest in psychiatry as a subject."

DISCUSSION

The needs most felt by students seems to have been (1) inpatients with whom they might work " from the diagnostic clinic to ultimate discharge ", and (2) the opportunity of seeing psychotherapy. From long experience of medical students we are inclined to regard the two requirements as the same; for the insufficiency of the student, when analysed, can be reduced to the problem of management in the psychotherapeutic situation whatever technique is used. There was a clear desire to see the *same* patient repeatedly, to learn to control the interview, and to have experience of the difficulties arising from it. The need for more teaching in psychotherapy is stressed in the memorandum by the working party of the College of General Practitioners and is clearly stated in the report of the British Medical Students Association. A need so widely felt is one that we must try to satisfy.

A desire for more teaching in the psychiatry of childhood was clearly evinced, and this was dealt with in the B.M.S.A. report too. Compulsory questions in psychiatry, set and marked by psychiatrists, is advocated by the general practitioners and by implication by the B.M.S.A. too, in their support of the Sheffield Plan. This question was not put to our own students, and we mention it only for completeness.

In all the four sources we have surveyed there is emphasis on the need for more time to be devoted to psychiatry; and for the integration of psychiatric and somatic medicine at an earlier stage in the clinical course. Our own students made the second point in question 10, and the B.M.S.A. in its report deals with the first one. It says: " The overall student opinion is to the effect that insufficient time is given to the teaching of psychiatry . . ." The General Medical Council in its recommendations of 1957 says: " During his study of all clinical subjects the attention of the student should be continuously directed by his teachers to the importance of the inter-relation of the physical, psychological, and social aspects of disease." Perhaps we may leave the last word with the general practitioners:

" To misdiagnose organic disease has long been considered a serious mistake; it is now being appreciated that to miss psychological illness is just as bad, and may lead to even greater unhappiness. So much of medical teaching is concerned with organs and tissues that many medical students, and some family doctors, tend to lose sight of the patient as a person whose anxieties, fears, griefs, rages, guilts and inadequate relationships with other people can, and do, make him ill . . . It is clear that greater emphasis needs to be placed on psychological medicine in the training of the undergraduate . . . It is thought that only 1% of the psychological casualties seen in general practice are referred to psychiatric specialists; and yet the psychiatric services are working to capacity, and nearly half the hospital beds in this country are already taken up with their patients. In future . . . general practitioners must be encouraged and trained to treat, adequately, a much larger number of these patients."

SUMMARY

1. 110 unsigned questionnaires filled in by Westminster Hospital students have been examined to ascertain their opinions about the pattern and adequacy of psychiatric teaching.

2. The students' views closely resembled those expressed by the British Medical Students' Association and by the working party of the College of General Practitioners.

3. The principal needs as seen by our own students were (*a*) more work with inpatients, (*b*) opportunities to see and perform psychotherapy, and (*c*) further teaching in the psychiatry of childhood.

4. Our students felt the need for more integration in the teaching of psychiatric and somatic medicine. The B.M.S.A. says the same thing in its undisguised admiration of the " Sheffield Plan ". In fact we feel quite integrated with our colleagues; but probably, from the student's point of view, the relationship is not brought to his notice quite early enough.

We wish to thank Dr. Peter Sainsbury, one-time chief assistant to the department, who collaborated with one of us (G. G.) in drafting the questionnaire. We must however exonerate him from any responsibility for our conclusions or recommendations.

We would also wish to thank our student friends for their cooperation in filling in the forms and for not yielding to base impulses when confronted by them.

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Special Articles

STEAM PENETRATION INTO CONTAINERS FOR SURGICAL DRESSINGS

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VARIOUS containers are available for holding surgical dressings during steam sterilisation and the period of storage before use. Their relative merits have been outlined (Fallon 1960), but no study has been made of the rate of steam penetration into loads within these containers. The modern high-pressure high-vacuum steriliser will reduce the differences in the rate of steam penetration into the various forms of container; but many hospitals still use downward-displacement sterilisers, and will continue to do so for some time. Accordingly, there is much immediate practical interest and concern about the different rates of steam penetration, especially into the newer types of container subjected to the downward-displacement method of steam sterilisation. Details of the principles and practice of this method are given in the report of the Medical Research Council's working party on pressure-steam sterilisers (1959).

Materials and Methods

Containers

Four types of container were studied: 1. A cylindrical dressing drum of 10 in. diameter × 9 in. deep. 2. A metal dressing box with built-in cotton-twill filters, of the same general design as that described by Thompson and O'Grady (1959) but measuring 12 × 11 × 11 in. 3. A cardboard box (Nuffield Provincial Hospital Trust 1958) measuring 6 × 10 × 10 in. 4. Packs wrapped in cotton twill, crepe paper, or nylon film.

Load to be Sterilised

This consisted of eight cotton huckaback towels, measuring 20 × 30 in., folded so as to present twelve thicknesses, and wrapped in a further two towels. These were placed inside the container so that in the steriliser the folds were vertical. In this way the towels presented least obstruction to the downward penetration of steam.

Steriliser

The 4·2 c.ft. horizontal dressings steriliser used for these experiments will be described in detail elsewhere (Fallon 1961). Here it suffices to say that instruments were arranged so that up to fourteen accurate temperature measurements could be made simultaneously at different points within the chamber. The steriliser was operated at 20 lb. per sq. in. (126°C). Mains steam at 60 lb. per sq. in. was led in through a separator and a reducing valve. The supply system carried an adequate flow of good quality steam, with a dryness fraction of 0·98 when measured by throttling calorimetry in the low-pressure (20 lb. per sq. in.) supply line.

Temperature Recording

The penetration of steam through the various containers and loads was recorded by thin thermocouples placed in between the towels. The number of thermocouples used for any single container ranged from 2 to 9, depending on the number of containers in the steriliser. These thermocouples were introduced from the bottom of the load to reduce the likelihood of steam tracking along them. They were placed in the same positions in each load (i.e., in the front, back, and middle towels).

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Procedure

Containers were placed in the steriliser so that they presented the least possible obstruction to downward displacement of air. If more than one container was placed in the steriliser at one time, the experiment was repeated with the relative positions of the containers reversed, so as to demonstrate any alteration in steam penetration due to the site of the container in the steriliser. As noted later, some of the findings in the experimental steriliser were checked in a larger (9 c.ft.) horizontal dressings steriliser, also operated by downward displacement of air.

Results

Dressing Drum

18 experiments were performed to determine the outside limits of the time required for steam to penetrate the drum (fig. 1). Heating up was rapid, in most cases requiring much less time than the upper limit shown. But a load of only eight towels plus two lining a drum of this size represents a very loosely packed drum indeed. Hence it is not surprising that steam penetrated rapidly into loads within this small efficient steriliser, which normally reached a pressure of 20 lb. per sq. in. in 4–5 minutes from the time of turning on the steam.

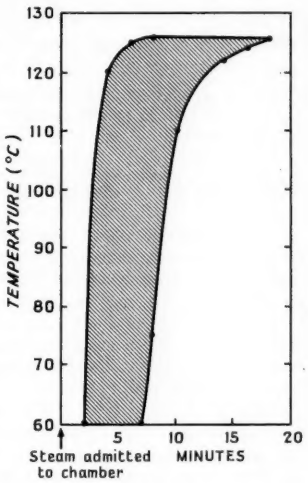

Fig. 1—Time taken for the coolest part of the load in a 10 × 9 in. dressing drum to heat to 126°C.
The shaded area represents the results from 18 experiments.

Metal Box

Fig. 2 shows the limits of the times required for the load in a metal box to heat to 126°C, as determined from 6 experiments. The load took much longer to heat up than when it was placed within a drum. It seemed possible that this was due either to the relatively large size of the metal box (11 in. deep) compared with the diameter of the experimental steri-

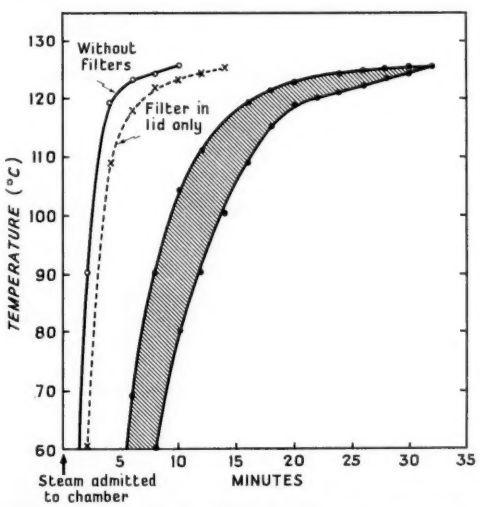

Fig. 2—Temperature rise to 126 C in the coolest part of the load in a metal box.
The shaded area represents the results of 6 experiments with filters in both the lid and base of the box.

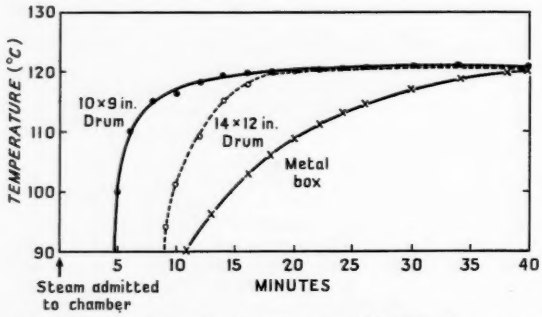

Fig. 3—Temperature rise of coolest part of load in three types of container in a 9 c.ft. steriliser working at 17 lb. per sq. in.

liser (16 in.), or to the greater amount of air to be removed from the metal box as compared with the dressing drum. (The volume of the metal box was 1452 c.in. compared with 707 c.in. for the dressing drum.) Consequently experiments were made in a 9 c.ft. horizontal steriliser to see the effect of a larger steriliser on steam penetration, and also to compare the speed of steam penetration through the metal box with that through a larger dressing drum (1847 c.in.). This steriliser operated at about 17 lb. per sq. in. Here also temperature recordings were made by thermocouples inserted in the load. 2 thermocouples were placed in the lower part of the third and sixth towels from the front of each container when placed in the chamber. The results of a typical experiment are shown in fig. 3. Both loads in drums heated up more rapidly than that in the metal box. The delay in steam penetration was obviously not due to the size of the metal box. The possibility remained that it was due to the filter material itself, and 2 further experiments were made: (1) with the filter material removed from both top and bottom of the metal box, and (2) with the filter replaced in only the top of the box. The results in fig. 2 show clearly that the delay in steam penetration was due to the closely woven filter material.

Cardboard Box

This was a standard cardboard box, as illustrated in the report of the Nuffield Provincial Hospital Trust (1958), obtained from the stock held in the hospital pharmacy. Thermocouples were introduced through small holes bored at the bottom of one side of the box. Care was taken when packing this container not to compress the load of towels. The results of a typical experiment in the small steriliser are shown in fig. 4. The results were similar in the 9 c.ft. steriliser. Steam always penetrated much more slowly through the load in the box than through that in a 10×9 in. dressing drum, but not usually so slowly as through the load in a metal box (see figs. 2 and 3).

Packs

Nylon film.—Loads of towels identical with those used in other types of container were placed in heat-sealed nylon bags, made from tubes of nylon lay-flat film. Two thicknesses of film were used, 0·001 and 0·002 in. (0·0254 and 0·0508 mm.) respectively.

(*a*) A preliminary experiment was performed to show that nylon film is, in fact, permeable to steam. Cotton huckaback towels were placed in nylon bags, and as much air as possible was expressed from the bags, which were then sealed with a heat-sealing machine. The bags were weighed and sterilised at 126°C. Pressure in the steriliser was reduced to that of the atmosphere, and the bags were removed and again weighed. Finally, to exclude the possibility that steam might have entered through defects in the seals, the bags were immersed in water to detect leaks. Bags always contained air on removal from the steriliser, and so leaks were easy to detect. The

WEIGHT OF HEAT-SEALED NYLON PACKS OF TOWELS BEFORE AND AFTER STEAMING AT 126°C WITHOUT DRYING AFTERWARDS

Experiment no.	Weight (g.)		Increase
	Before steaming	After steaming	
1	702	732	30 (4·2%)
2	511	531	20 (3·9%)

results of experiments where the bags showed no leaks after sterilising are shown in the table. The weight increase is of the same order as that in towels sterilised in drums and weighed in the same circumstances. These experiments demonstrate, therefore, that steam penetrates nylon film freely.

(*b*) The nylon packs used to determine the rate of steam penetration were sealed with a heat-sealing machine except for a small hole at the bottom of the pack through which the thermocouples passed. This hole was sealed as tightly as possible with heat-seal tape. In 5 of 6 experiments the load required 6–18 minutes longer to heat up than in a 10×9 in. dressing drum; a typical result is shown in fig. 5. In the other experiment the time was about the same for each container. In view of the free passage of steam into the load, as in the preliminary experiments, and also of the presence of air in sealed nylon bags taken from the steriliser, the slow rise in temperature was probably due to an air-steam mixture forming in the bags.

Cloth.—Packs were wrapped in a double layer of cotton twill.

Paper.—An experimental crepe paper, designed as an outer wrapper for packs, was used in thicknesses of one or two layers. The results of tests where these packs were sterilised together with a similar load in a 10×9 in. dressing drum showed little difference in the time required for the loads to heat up, but the drum load usually heated up slightly more quickly than that in a double-wrapped pack. Wrapping a pack in one layer of paper instead of two rendered steam penetration more rapid; so did removing the pack wrapping altogether. It is important to note that the eight towels in a dressing drum were probably lying more loosely than those in the packs, purely because it is difficult to make up a pack very loosely.

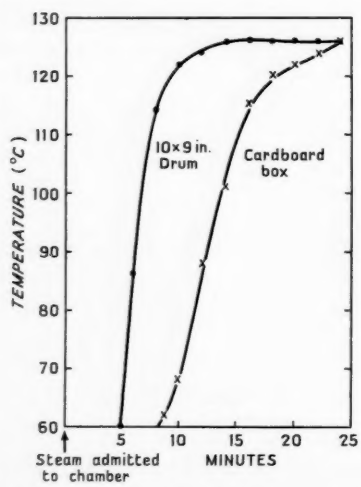

Fig. 4—Temperature in the coolest part of the load.

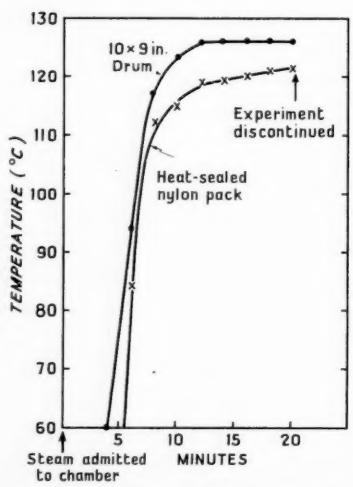

Fig. 5—Temperature in the coolest part of the load.

Discussion

These findings are presented to warn those using downward-

displacement sterilisers that the time required for steam penetration into different types of container varies with the container as well as with the load. Penetration will also vary with the efficiency of the steriliser. Even with loosely packed loads of the type used in these experiments, metal boxes with filters may seriously interfere with steam penetration; and obviously, if the containers are tightly or incorrectly packed with respect to the flow of steam, sterilisation may not be accomplished. Similarly if cardboard boxes are badly packed, or perhaps stacked on top of one another, sterilisation might fail. Nylon seems to be an unsuitable material for wrapping packs because it seriously interferes with the heating up of a load, probably by air retention. Although there are other ways of sealing nylon so that air might perhaps escape, it seems undesirable to use an air-impermeable material in a steam steriliser. Like others (e.g., Darmady 1959), I have found that nylon film tends to become brittle on repeated use. It is not easy to seal completely by heat, particularly after it has been sterilised, and holes are difficult to detect—a criticism applicable to any transparent wrapping and also to paper.

No doubt packs wrapped in fabric, or perhaps paper, have advantages over dressing drums, not only because it is difficult to overpack in the way that a drum may be overpacked but also because packs offer much better protection to their contents than do unlined and damaged dressing drums. Dressing drums should be lined, with a fitted lining (Fallon 1959) if necessary, and they should be replaced as soon as possible by packs, or perhaps other types of container. When high-vacuum sterilisation processes are used there are no differences in the steam-penetration times of the various containers, and other criteria are needed to decide which type of container should be used (Fallon 1960). Nylon, however, again has disadvantages because sealed bags burst under high vacuum unless their air content is small.

When properly applied with really loose packing in a well-designed steriliser which has been tested and, if necessary, adjusted to guarantee its efficiency, downward displacement of steam is a successful sterilising procedure. But wherever possible the high-vacuum method of sterilisation should be used because it alone can deal with even mild degrees of overpacking and difficulty of steam penetration through the many different containers used in hospitals.

Summary

The rate of steam penetration through similar loads in the various containers commonly used for holding surgical gowns and dressing has been investigated.

Any container increases the penetration-time compared with that of the unwrapped load. Nylon film delays steam penetration because of retention of air rather than because of resistance to steam penetration, and it is therefore a dangerous wrapping material. Ignorance of the variations in steam-penetration times can be dangerous.

My thanks are due to the board of management for the Western Infirmary, Glasgow, for a grant from their endowment funds towards the cost of equipment. The metal box was supplied by Messrs. Sierex, Ltd., and the experimental crepe wrapping paper by the Bowater-Scott Corporation, Ltd. The drawings are by Mr. R. Callender.

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Points of View

THE SIGNIFICANCE OF DISC LESIONS

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M.R.C.S.

NO-ONE who compares the absence of disc lesions from the diagnostic repertoire of the physicians of the 1930s with their two-a-penny appearance in the 1950s (in the table published by Morris,[1] for example) can fail to entertain some doubts about the value of this diagnosis. The regrettable fact is that a pathological phenomenon of doubtful clinical significance is now current idiom to both general public and medical profession alike. " Slipped disc " has become almost a synonym for " sore back ", and when the words " disc lesion " are used it is practically impossible to make out what is wrong. There are two ways of arriving at the diagnosis. The first is the easy way—the facile orthodox habit of referring to all spinal disorders of mechanical origin as disc protrusions, particularly when there is referred pain; even neurologists do it. The other way is less easy because it involves taking a careful history of the stresses and strains to which the patient has been and is subject, and examining the mechanical efficiency of individual spinal joints and any other joint which may be concerned. But if you doubt the value of diagnosing disc lesions, then logically there is no escape from this.

* * *

The normal disc is adequately described in standard textbooks. It serves functionally as a cross between a cushion and a shock absorber—a function which, incidentally, has been shown by Roaf [2] to be shared with the cancellous bone of the vertebral body. When healthy, the disc is very tough. Any injury which would damage it would also cause considerable bleeding, and would probably be accompanied by fracture of part of the vertebra. An injury affecting a healthy disc alone is almost impossible. Pathologically the only important thing which happens to it is degeneration. But before considering the various consequences of degeneration, it would be sensible to think for a moment about why the disc degenerates.

Postmortem studies have revealed that all discs degenerate to some extent with advancing age, but some of them do it more quickly than others; and it is these that concern us. The disc is too tough to be damaged by the ordinary stresses and strains to which we are subject, so how does the process of degeneration begin? Unfortunately neither my pathology [3] nor my physiology [4] textbooks do more than describe it, and they make no attempt to say why it happens. So in the absence of expert advice, one is left to guess that the most likely cause of degeneration is local circulatory failure—or at any rate partial failure. We know that it is possible for one disc to become completely obliterated, and that the discs on each side can remain perfectly healthy. Thus, if the circulation has anything to do with it, this must be a purely local effect—a segmental effect. There are two possibilities: either there is local obstruction to drainage or local obstruction to supply—or

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2. Roaf, R. *J. Bone Jt Surg.* 1960, **42B**, 810.
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both. Drainage can be obstructed to some extent by local loss of mechanical function (that is to say loss of movement between two vertebræ) and to a greater extent by œdema. The blood-supply can be reduced by vasoconstriction caused by reflex sympathetic irritation involving one neurotome. However, though it is unlikely that any one of these factors could start the process of degeneration by itself, it is possible that in combination they might do so, provided that the time factor is added. Local circulatory failure alone can cause degeneration if it goes on long enough.

* * *

The next problem is whether these factors can obtain in a spinal segment, and if so, why? Probably the circulation of the intervertebral tissues depends on segmentally arranged arteries with segmental innervation, whereas other parts of the body can rely on a liberal collateral circulation. Some authorities refer to a degree of overlap of segmental innervation,[5 6] and to arterial intersegmental anastomosis.[7 8] This has to be accepted, but the context of its application is the healthy spine. The pathological lesions caused by the injuries and strains to which the spine is subject are characterised by segmental involvement. Loss of mechanical function, capillary dilatation and œdema, and a source of reflex nerve irritability, are features of any joint sprain. In the spine, a simple sprain involving the two intervertebral joints will produce these features, but they will be limited to the tissues of one intervertebral segment. This happens quite often, and radiographically it is commonplace to see isolated narrowing of intervertebral spaces.

When such an injury is severe, the local inflammatory reaction spreads from the intervertebral joints to the ligamentum flavum, the intertransverse and interspinous ligaments, the posterior longitudinal ligament, and the posterior part of the annulus fibrosus. If the joint lesion does not heal properly, or if it becomes chronic and the loss of function remains, then the local neurocirculatory failure will begin to take effect. The joints and the ligaments mentioned, as well as the posterior part of the annulus, are all supplied by the spinal artery which enters the spinal canal via the intervertebral foramen. Thus, if neurocirculatory failure affects them for long enough, degeneration is bound to follow in due course. This is one of the reasons why the posterior part of the annulus shows signs of degeneration more often than the anterior.

The effect of this will extend beyond the skeletal structures supplied by the spinal artery, which also supplies the cord and the meninges. Because the cord is supplied indirectly via the anterior and posterior spinal arteries, it is not subject to segmental circulatory deficiencies. But the nerve-roots and their meninges, and the spinal nerve-trunks, all receive a segmentally arranged arterial supply, and hence they too are subject to circulatory deficiencies. This may explain how some cases of " neuritis " arise.

* * *

When degeneration of a disc begins, it has been shown by Hendry that the hydration of the nucleus is reduced progressively [9] until the process is complete, by which time the nuclear tissue is dried up, and the space narrowed. As this process goes on, the disc becomes less and less efficient. At the same time the ligamentum flavum and the interspinous ligaments become less elastic and more fibrous; the joints become stiffer; and the bone round the intervertebral joints and the vertebral bodies (where bone and cartilage are united) becomes the seat of osteochondrotic or sclerotic proliferation which results in osteophyte formation. There is every reason to suppose that the pathological process of degeneration and prolapse of the intervertebral disc can occur without causing any symptoms at all, the herniated nucleus becoming absorbed. Indeed in many cases of chronic sacroiliac strain the symptoms have never indicated lumbar involvement, although X-rays reveal that degeneration secondary to the sacroiliac lesion must in fact have taken place. Radiological, pathological, and myelographic studies by McRae [10] showed that the incidence of disc protrusions in patients with and without symptoms was similar, while studies by Falconer et al.[11] showed, when myelograms were repeated after the symptoms had gone, that the appearance of the disc protrusion remained unchanged.

We have already noted that the annulus is insusceptible to injury when healthy; but this is also true when it is completely degenerated. By then it is unlikely to become the seat of inflammation because, having no longer any function, it cannot easily be injured. The disc is most vulnerable, both to injury and secondary inflammation, when degeneration has begun but some function still remains. But it must be emphasised that the basic lesion affects the whole vertebral segment, and that the involvement of the disc is purely incidental.

To defend this simple explanation against attack, I have to reply from clinical experience. The lesion that is postulated—a simple joint sprain with local loss of function, reflex muscle spasm, and pain—is very common.[12–14] It can be due to injury or chronic mechanical strain, or it can be viscerosomatic or psychosomatic in origin. Clinically the loss of joint function between vertebræ is clearly objective; so is the muscle spasm, and so is one other sign —namely, the increased sweat-gland activity of the dermatome involved, with skin temperature raised in the acute stage and lowered in the chronic. All these signs are not necessarily present together, but they usually are. And anyway the picture is so common that clinically there is no doubt. Far and away the most important of the physical signs is the mechanical loss of function, because in the simple uncomplicated lesion not merely the subjective symptoms but the signs themselves are resolved as soon as function is restored. Anybody, therefore, who intends to attack this explanation will have to explain away some precise and objective clinical signs.

There are no clinical signs of disc inflammation. Despite what is known of the pathology of the disc, there is no sign or combination of signs pointing to the disc and to nothing else. One symptom, however, is indicative, and that is deep local pain when the abdominal pressure is raised suddenly (as in sneezing or coughing), or when it is raised strongly by the simultaneous contraction of abdominal muscles, hip flexors, and erector spinæ (as when a patient with acute lumbago tries to sit up in bed). But pain on sneezing is not pathognomonic of inflammation of the annulus; there are other causes. However it is a reasonable supposition if the other possibilities are excluded, and if the history and clinical picture point that way.

* * *

5. Pedersen, H. E., Blunck, C. F. J., Gardner, E. *J. Bone Jt Surg.* 1956, **38A,** 377.
6. Stilwell, D. L. *Anat. Rec.* 1956, **125,** 139.
7. Amato, V. P., Bombelli, R. *J. Bone Jt Surg.* 1959, **41B,** 782.
8. Harris, R. S., Jones, D. M. *ibid.* 1956, **38B,** 922.
9. Hendry, N. G. C. *ibid.* 1958, **40B,** 132.
10. McRae, D. L. *Acta radiol.* 1956, **46,** 9.
11. Falconer, M. A., McGeorge, M., Begg, A. C. *J. Neurol. Psychiat.* 1948, **11,** 13.
12. Glover, J. R. *Lancet*, 1959, i, 1165.
13. Dalgleish, P. H. *Med. Proc.* 1959, **5,** 24, 523.
14. Stoddard, A. Manual of Osteopathic Technique. London, 1959.

So far I have not said much about disc protrusions for the simple reason that clinically they seldom matter very much. There are plenty of possible, and logical, causes of nerve involvement secondary to spinal lesions of mechanical origin. Hence there is no excuse for making the facile assumption that they are all due to something pressing on a nerve, particularly in the light of Kelly's papers on the subject.[15 16] Even though we know that disc protrusions do occur, there are no positive clinical signs to indicate that they have done so. This is hardly surprising since they can happen without causing any symptoms or disability. The incidence of disc protrusions has been shown to be similar in patients with and without symptoms.[10] Furthermore pressure on a nerve after an injury is much more likely to be due to inflammatory œdema. Occasionally the disc protrusion is clinically significant; but the only situation in which this can be presumed is when paralysis persists after a spinal injury. Probably what happens in these cases is that the herniated nucleus presses a fragment of ruptured annulus into the intervertebral foramen.

X-rays do not tell us very much about a disc except the degree of narrowing between vertebral bodies, from which one can infer the progress of degeneration. Lumbar puncture, and the introduction of contrast medium to show filling defects, have been studied by Lansche and Ford,[17] and shown to have limited accuracy. It is impossible to distinguish between an œdematous annulus, a herniated nucleus, a tumour, or anything else, merely by looking at a myelograph. Certainly it cannot show whether the thing that causes the filling defect is actually damaging nerve tissue. Nor for that matter is nerve damage necessary for a disc to acquire surgical significance.

There is sometimes a tendency to slide into the diagnosis of a " slipped disc " merely because conservative treatment has failed. One is apt to forget that the only purpose of diagnosis is to help in deciding what is to be done for the patient, and there is no point in making a diagnosis the treatment for which is purely operative if there is no intention of operating. There may very well be a disc protrusion, but if it is not responsible for the symptoms it is of little help to the patient to make that diagnosis. After all, most of us have disc protrusions sooner or later, but generally they don't matter.

15. Kelly, M. *Neurology*, 1956, **6**, 32.
16. Kelly, M. *Med. J. Aust.* 1960, i, 118.
17. Lansche, W. E., Ford, L. T. *J. Bone Jt Surg.* 1960, **42A**, 193.

" . . . It is common among medical historians to lament the decline in the practice of medicine during the period which extends from the sixteenth to the very middle of the nineteenth century. They despair of the blood-letting and purging, of the unbridled use of emetics, and of the therapeutic and pharmacological jungle in which the physician wandered as one both deluded and blind. That the practice of medicine was indeed in a degraded state, cannot be denied. But it is, I submit, the historian's obligation to understand rather than to blame. And this period is not difficult to comprehend. It is a transition period, one in which the old was discarded and the new not yet brought into being. Men do not attain to knowledge or wisdom in a single leap, they grope for it, and groping they often wander far from the mark. Were all the theorists and system makers fatuous and futile? Were they not rather earnest men grappling with the unknown? And how many among those we celebrate as the true scientists derived their inspiration, be it only in a negative pattern, from those others who before them had made the wrong guess, or hypothecated an erroneous theory? I am inclined rather to regard this period as heroic in spirit, even if modest in accomplishments."—Dr. IAGO GALDSTON. *Bull. Hist. Med.* 1961, **35**, 50.

In England Now

A Running Commentary by Peripatetic Correspondents

As I made my way in the early morning on St. John's Day to the Priory Church at Clerkenwell, the nearby streets were almost deserted and their shabbiness only too evident in the absence of normal business activity. Then I turned the corner and the scene was transformed. In front of me stood the ancient gate house, gay with banners flying from its twin towers. And when I joined the large congregation assembled in the crypt to celebrate the patronal festival of the Order of St. John of Jerusalem, the contrast between the modern commercial world and the age of chivalry was complete, for the church, in the ordinary way silent and empty, was filled with people dedicated to unworldly ideals. Of course the revival of the order in this country during the last century is often dubbed another piece of sham Gothic, but even if this were wholly true—and it is not—the proceedings at the general assembly would be enough to make clear the religious foundation on which it rests. The Cross carried before the procession of knights and high officers of the order, each in his mantle bearing the eight-pointed Maltese cross, the prayers at the beginning and end of the session, and the report on the order's pious and charitable works all bear witness to the principles by which it is moved. And if any doubt should remain, they would surely be dispelled by the tremendously impressive commemoration service in the afternoon when there was hardly an empty seat at St. Paul's Cathedral.

* * *

" Of all my Wicked Uncles," said Ananias, " Uncle Charlie was probably the least dishonest; he was a villain and he looked like one. As a financier he took so much interest in, and from, the companies he promoted that, on his sudden departure overseas, he was missed, luckily for him, by a great many people including the fraud squad.

" Several years of hard work, mostly other people's, brought him much wealth and an ulcer dyspepsia for which laparotomy was advised. After someone had told him about our National Health Service, and after they'd convinced him they weren't pulling his leg, he decided to fly back to Mother England, the Great Giver of All, and get his repairs done for free.

" Reading between the lines of my infrequent letters—come to think of it, my writing is so bad that was probably the only way he could read them—he had got the impression that I pretty well ran London's major hospitals, and I was therefore told to get him admitted somewhere forthwith. There seemed about as much hope of this as of getting Khrushchev into the Carlton Club, but after some thought I passed the word round that Uncle was a diamond smuggler whose technique was to swallow them, and as there had recently been a deficit shown on his intake/output chart, his symptoms might be due to chronic retention.

" The moment Uncle arrived, I premedicated him q.q.h. with bits of costume-jewellery made up inside pills, and the X-rays showed more cut-glass than a chandelier. The *res ipsa loquitur* was such that I could have auctioned him off at Sotheby's, but I finally sold the mineral rights to the MacGrolloch syndicate for £50 cash down and £50 post-operatively. MacGrolloch decided matters were so urgent that he'd better do a transverse incision to save time unbuttoning Uncle's waistcoat. However, when the prospectors had reached the diamond-bearing stratum, the suction apparatus somehow got turned on full and the whole collection was sucked into the pipe. The syndicate left the theatre at the double, all except the first assistant whose finger got stuck in the spout, but everything had disappeared into the hospital's drainage system.

" MacGrolloch was so furious he ' cried copper ' on Uncle Charlie, who awoke to find his bed knee-deep in policemen and expired from shock. I never got my second £50, and after I'd settled with the technician in charge of the suction apparatus the balance was so small that I feel sure Uncle would have been disappointed."

Letters to the Editor

DETECTION OF LUNG CANCER

SIR,—Lung cancer—the growth that tolls most bells of all malignancies—was the subject of your leading article of June 3. This prompts us to write of our current work, giving some interim observations.

The South London Lung Cancer Study* which started on Dec. 8, 1958, aims to investigate the natural history of the disease and assess the place of serial routine radiography in its earlier detection.

For the study the six units of the South East and South West London Mass X-ray Services offer all males over 45 (excluding general-practitioner referrals) appointments for six-monthly 100 mm. chest films.

The volunteers know the purpose of the procedure. With their cooperation 99,426 individual examinations have so far been made. 44,298 were first examinations under the scheme. These yielded 57 cases of malignant pulmonary neoplasm—i.e., 1·3 per 1000 examinations.

The 55,128 repeat examinations led to the discovery of 35 cases—i.e., 0·64 per 1000 examinations.

It will be seen that the yield on induction is twice that found on repeat examinations. This suggests, as would be expected theoretically,[1] that the un-X-rayed population at any time contains a considerable proportion of cases of more than six months' radiological duration—i.e., the lower yield at the repeat examinations is due to the first examination having skimmed off the accumulated pool of slower-growing cancers.

The 55,128 repeat examinations (each made six months after a previous one) represents 27,564 man-years of observation of people whose initial films were considered to be clear. The yield of 0·64 per 1000 six-monthly examinations represents 1·28 growths per 1000 man-years of observation.

We do not yet know the total number of cases of lung cancer occurring annually in our volunteers because there must be a proportion of cases which develop and fall out clinically during the inter-survey intervals (these may be traceable later from area cancer registrations). However, we can obtain by calculation (from data in the Registrar General's Statistical Review of England and Wales, Part I, Tables Medical, 1956) the expected deaths from a group of Greater London male residents equal in number and age composition to our volunteers. The expected number of deaths found in this way is 56. To get the number of *cases* occurring in this population we must add to the 56 expected deaths the expected number of survivors. Assuming a survival-rate of 6%,[2] there would be 4 survivors. Therefore, in the calculated Greater London population equivalent to our examinees there would be an occurrence of 60 cases per annum. In fact we found 35 out of this 60 cases expected to occur in the surveyed population—i.e., 58%. *The likelihood that almost two-thirds of all cases of lung cancer occurring in a population may be found by this routine procedure suggests its high value as a cancer-detection measure.*

This statement about diagnostics is independent of the current position in therapeutics. The importance of this finding, if confirmed, is that the majority of lung cancers occurring in a population are demonstrably present even on examinations conducted only twice a year. The observation has an importance in its possible application to non-radiological cancer—detection tests—e.g., to serological techniques which may be evolved in future.

Resection.—The Brompton series of lung-cancer patients [2] had a resection-rate of 23%. (Our experience with symptomatic patients referred to the mass units by general practitioners is similarly disappointing. Of 122 cases of lung cancer found among patients referred to our units by their doctors, 27 [22%] were resected.) Of the 57 cases of lung cancer found so far on the induction examinations under the South London Lung Cancer Study 32 (56%) were resected. Of 35 cancers found on the subsequent (six-monthly) examinations for the study 18 (52%) were resectable.

The similarity of resection-rates in cases found on first examinations and subsequent examinations is explicable on the theoretical grounds we gave earlier—that the ratio of fast-growing to slow-growing neoplasms differs in the "repeat" group from the "initial" group in that there is a greater proportion of fast-growing cancers in the repeat groups. Indeed, one could anticipate that the shorter the interval between routine examinations the greater would be the proportion of fast-growing cases that would be found.

When we shorten the interval between examinations we introduce two opposing factors in the prognosis of the groups: (*a*) the effect of earlier diagnosis obtained by shortening the inter-survey interval; and (*b*) the effect of the introduction of more rapid-course bad-prognosis cases into the group.

We have no information yet about survival of cases found at six-monthly examinations and it will be some years before any final conclusions about the value of examinations at this particular interval can be reached.

A simple accurate serological test for cancer that could be used in synergy with radiography for pre-symptomatic diagnosis at periodic routine mass examinations is sorely needed. No would-be public benefactor could spend his money better than to offer a prize of £100,000 to the first workers who develop such a proved test. "Give us the tools . . ."

South West London Mass X-ray Service, Western Hospital, Seagrave Road, London, S.W.6.

FIRMIN NASH
MANSEL MORGAN
GARRICK TOMKINS.

* Made possible by research grants from the South West and South East Metropolitan Regional Hospital Boards.

1. Nash, F. A. 3rd International Congress of Medical Radiography, Stockholm, 1958; p. 306. Rome.
2. Bignall, J. R. Carcinoma of the Lung; p. 169. Edinburgh, 1958.

INTENSIVE-CARE UNITS IN AMERICAN HOSPITALS

SIR,—Dr. Buxton Hopkin (Feb. 4) describes an American example of a "recovery room" in which patients spend a few hours or days after operation. But, if a trend is evident in the United States, I would say that it is toward the establishment of intensive-care units rather than recovery rooms. In the larger hospitals there may be two such units, medical and surgical; but in smaller hospitals both medical and surgical patients often receive intensive care in one integrated unit.

In this hospital of 400 beds, opened last June, we have a 20-bed medical unit adjacent to the medical floor, plus a combined post-anæsthesia surgical unit of 20 beds beside the operating-theatres. This is by no means a unique arrangement, and many similar units will be in use as new hospital construction permits.

The surgical intensive-care unit may be regarded as a development of the recovery room, as described by Dr. Buxton Hopkin; but it differs in that it may hold cases for as long as five days before they are transferred to an ordinary nursing ward.

The patient who requires the closest observation and the most skilled nursing care is admitted to, or transferred to, the intensive-care unit. When his condition improves, he is moved to a room elsewhere in the hospital, where he gets ordinary nursing.

The principle underlying this arrangement is that the patient is assigned to the part of the hospital which is best suited to his needs, and where his fellow patients have similar needs and capacities. Since the number of trained nurses, and of their assistants, varies according to the work to be done, nursing skill can be used much more economically.

Naturally, the intensive-care units have immediately accessible equipment and drugs for use in emergencies. Any critically ill patient, regardless of the service under which he was or is admitted, may be directly admitted or transferred to them (the exception being children under 13, who go to pædiatric wards); but efforts are made to keep one bed in reserve at all times. In our hospital, each intensive-care unit has from two to three times the nurse staffing of regular-care units. Besides a head nurse (ward-sister), we maintain an average of one trained nurse and one non-professional helper for every five or six patients. The staff are assigned to the unit permanently, but new personnel can be rotated through the unit to provide a constant patient-nurse ratio.

Memorial Hospital of Long Beach, Long Beach, California. DONALD C. CARNER Administrator.

PSORIASIS

SIR,—Your leading article of June 10 repeatedly refers to the skin lesion of psoriasis as inflammatory. Is this correct?

The widely dilated and tortuous capillary loops seen in this disease are peculiar to psoriasis and are not seen in inflammatory processes. This has been especially shown by Gilje's capillaroscopic studies. Recent work has further shown that there is indeed a generalised abnormality of skin capillaries, not restricted to the erythematous areas. Moreover, the surface temperature of psoriatic plaques is often not significantly raised, indicating that although capillaries are dilated the blood-flow is not increased. This and other less conclusive evidence all points against psoriasis being an inflammatory lesion.

If this remarkable vascular lesion is not dismissed as inflammatory it may lead to a better eventual understanding of psoriasis than a concentration (perhaps overconcentration) on biochemical findings.

London, W.1. F. RAY BETTLEY.

PUBLICATION—BUT HOW?

SIR,—I read your recent leading articles and the letters under this heading with considerable interest, following my own earlier comments on other aspects of the same general subject.[1]

Our problems in this respect are essentially those of the overproduction of consumer goods. The primary purpose of scientific publication is the dissemination of information—a statement which may surprise many of our present-day authors, who tend to be preoccupied with the propitiation of selection committees or by considerations of departmental prestige. Nevertheless, articles are presented to be digested by one's colleagues, and, by virtue of this, may be fairly described as " consumer goods "—which are, furthermore, perishable to a degree. There is a time limit for most articles beyond which their subsequent publication becomes increasingly pointless.

I would also suggest that the frequent emphasis which has been laid on the individual excellence of the multitude of articles being currently submitted arises from some confusion of thought on fundamental issues. A glut is a glut, irrespective of the standards of quality of the goods concerned, and, indeed, the very fact of this uniformly high standard intensifies the crisis. As to any solution, that I fear will hardly be achieved by any device of editorial ingenuity, but will impose itself on us in accordance with natural laws. We are, after all, concerned with a self-perpetuating cycle. The germination of the resolve to prepare an article arises from the interaction of personal experience with the study of current literature, and when it finally appears in print it takes its place in the general body of medical literature, in which it in turn can contribute to the stimulation of other workers, by whose subsequent activities the cycle is repeated.

1. McClure, D. M. *Lancet*, 1960, ii, 1388.

In such a process, therefore, the " back pressure " effects of an editorial bottleneck may be readily deduced, but I think that we should be gravely mistaken if we were to imagine that if only facilities for publication could be doubled all would be well. I make this assertion because there is another level of obstruction involving the consumer, and even though the existing channels of publication are inadequate to satisfy the demands of aspiring authors they already far exceed the capacity of the individual worker to assimilate the journals piling up around him. An element of apparent inconsistency arises here, since a self-perpetuating cycle of work and publication should also be self-regulating; and the source of this lies in the present-day dictum of Publish or be Damned, by reason of which so many of those who seek the printed page are prompted not by having something to say but by the need to say something—and when I look back over the years I make no claim to freedom from personal guilt.

However, it seems that in the course of crying out in the wilderness my steps have carried me in a full circle and I am crossing a path I have already trodden. May I conclude therefore by remarking to those who clamour for a greater outlet for their literary flow, that the removal of an enlarged prostate can offer little benefit when the patient is also suffering from a urethral stricture and chronic nephritis?

South Shields. D. M. MCCLURE.

CHROMOSOME DAMAGE IN AN INFANT AFTER DIAGNOSTIC X-IRRADIATION

SIR,—Dr. Stewart and Dr. Sanderson (May 6) reported a probable dicentric chromosome in 2 out of 31 cells in a leucocyte culture from a patient with Klinefelter's syndrome who had received diagnostic radiation a few hours before the blood sample was taken. They cautiously suggested that the abnormal chromosome might alternatively be due to background irradiation or have developed in culture, or be related to the patient's abnormal karyotype (47/XXY). Leucocyte chromosome abnormalities may occur after therapeutic irradiation,[1] high therapeutic levels of radioiodine,[2] and treatment with nitrogen mustard.[3]

In November, 1960, a 7-week-old infant was admitted with multiple congenital anomalies. Among the investigations were six radiological examinations over a six-week period which included three of the chest, one of the abdomen, one of the cervical spine, and an intravenous pyelogram. A total of 22 X-ray exposures were needed for these examinations and because of the small size of the infant, the great majority covered a large proportion of the body area.

In January, 1961, chromosome studies were made on marrow and blood cultures because of the multiple anomalies. The counts showed a modal number of 46 but a higher incidence of non-modal counts than has been normally seen at this laboratory. In addition, definite structural chromosome abnormalities including dicentrics and probable chromatid deletions were recognised. Publication of this case was delayed since it seemed advisable to repeat these cultures after recovery from the effects of this radiation since no pre-X-ray control was taken; but the child had since died from the effects of the severe anomalies.

The purpose of this communication is to substantiate the report of Dr. Stewart and Dr. Sanderson. Full details of this case, including X-ray dose measurements, will be published shortly.

Research Institute and the Department of Pathology, The Hospital for Sick Children, Toronto. P. E. CONEN.

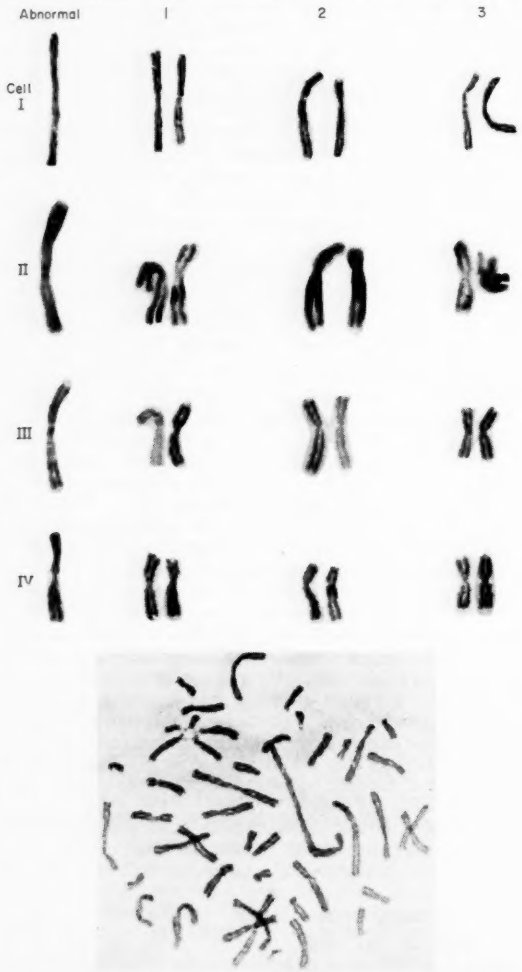
1. Tough, I. M., Buckton, K. E., Baikie, A. G., Court Brown, W. M. *Lancet*, 1960, ii, 849.
2. Boyd, E., Buchanan, W. W., Lennox, B. *ibid.* 1961, i, 977.
3. Conen, P. E., Lansky, G. S. In preparation.

CHROMOSOMAL ABNORMALITIES IN WALDENSTRÖM'S MACROGLOBULINÆMIA

SIR,—The report of Bottura and his colleagues (May 27) on a chromosomal abnormality in Waldenström's macroglobulinæmia prompts us to report briefly a similar finding in a proven case of the disease. Detailed studies on additional cases and also cases of multiple myeloma will form the subject of a subsequent report.

The patient was a 32-year-old white woman with ill-defined symptoms of lassitude and occasional episodes of fever. Study of peripheral blood revealed mild anæmia, a white-count around 4000, and a consistently and markedly increased erythrocyte-sedimentation rate. The bone-marrow showed normal cellularity with 2% plasma cells. The serum was not anti-complementary and did not contain lupus or rheumatoid factor. The total protein was 9·8 g. per 100 ml. with an increased γ-globulin. Ultracentrifugal analysis showed that approximately 25% of the total serum-protein was macroglobulin. Most of it had a sedimentation-rate of about 19S and there was also a minor heavier component with a sedimentation-rate of about 28S.

Marrow aspirated from the sternum was placed in short-term cultures but provided only ten cells suitable for chromosomal analysis. Four definitely contained 46 chromosomes, four probably 46, and two probably 47. Nucleated blood-cells were cultured, and of the ninety excellent metaphase figures scored, one had 45 chromosomes, eighty-six had 46, and four (4·4%) had 47 chromosomes. Multiple karyotypes of cells with a complement of 46 showed no abnormality. Each of the four blood-cells with 47 contained an extra abnormal chromosome of great length. Karyotypes were prepared from each of these latter cells; in two, except for the extra chromosome, no other abnormality was noted, but in two there was some difficulty arranging the pairs. The abnormal chromosome was seen in two other cells from which accurate counts were not possible. It consistently appeared exactly mesocentric, the arms being equal to or slightly longer than the longest arm of any other chromosome of the complement. Its density under phase contrast, in comparison to others of the complement, indicated no unusual degree of uncoiling. The exceptional length suggests that it may be an isochromosome possibly derived from the long arms of chromosome 2. Other explanations are of course possible.



Below: metaphase in nucleated blood-cell containing an unusually long abnormal chromosome. Above: chromosomes from four cells showing the abnormal chromosome in relation to group 1-3.

The abnormal chromosome found in this patient is indeed the longest we have observed in a human cell. Its proportions in relation to chromosomes of group 1–3 (the A-group of Patau) are shown in the accompanying figure. The abnormal chromosome pictured by Bottura et al. also had very long arms but differs markedly in centromeric position and in total length.

These observations suggest a possible identity between the population of cells having an abnormal chromosomal complement and the cells that produce excessive quantities of high-molecular-weight γ-globulin. That the abnormal chromosome differs in morphology in different cases of macroglobulinæmia probably indicates absence of a constant chromosomal aberration. The possibility exists however that similar portions of a specific chromosome, perhaps the long arm of 2, may be involved in each case. Alternatively, the chromosomal variation could be secondary to whatever causes the high-molecular-weight protein production in macroglobulinæmia. Studies of additional cases of macroglobulinæmia can be expected to help to elucidate this problem.

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CHROMOSOME ANALYSIS FROM SMALL VOLUMES OF BLOOD

SIR,—Lymphocyte culture for chromosome analysis, which has been widely used since Nowell's [1] observations on the induction of mitosis with phytohæmagglutinins, has the great advantage of being both quicker and technically simpler than fibroblast culture and less unpleasant than marrow biopsy. The conventional methods,[2] which have been responsible for the recent major advance in the study of human malignancy,[3] have the occasional disadvantages that the blood has to be processed within a few hours by a procedure which requires both experience and heavy equipment, and that the amount of blood is more than can easily be spared by babies or easily acquired from children, particularly under home conditions.

To overcome these difficulties we have been using a technique of lymphocyte separation which has now given satisfactory results for three months (our experience excludes leukæmia). While no originality is claimed for such simplicity, its practicality may merit publication.

Blood is drawn into a 5 ml. syringe containing one large drop of heparin. If practicable, 5 ml. is obtained. The syringe is

1. Nowell, P. C. *Cancer Res.* 1960, **20**, 462.
2. Moorhead, P. S., Nowell, P. C., Mellman, W. J., Battips, D. M., Hungerford, D. A. *Exp. Cell Res.* 1960, **20**, 613.
3. *Lancet*, 1961, i, 433.

sealed by sticking the needle into a cork or replacing the needle guard on a disposable syringe (we strongly recommend the 'Hypak' [705 DN] disposable syringe and needle; available through Arnold R. Horwell, London). The blood is mixed by horizontal rotation and the syringe is left, slanting or vertical, needle upward, for 1–2 hours at room temperature. The first 1 ml. of supernatant present is then ejected into a culture vessel after bending the needle. The usual concentration is 6–12 million leucocytes per ml. Counting is an additional safeguard but unnecessary in the absence of acquired disease, pregnancy, or recent pregnancy. The optimal inoculum appears to be between 5 and 15 million cells. The concentration of the last drop should be multiplied by a gradient factor of about 2/3.

If the syringe is left several hours, either by negligence or necessity, excessive leucocyte sedimentation may occur, and the syringe should be shaken and the separation started again. After 2 hours without resuspension, white-cell clumping is likely. Even the most violent agitations from travelling by car, or on foot, do not seem to reduce the sedimentation-rate. Incubation of the culture vessel may be delayed with impunity, and this is preferable to delay in separation. In our two experiences of blood which did not sediment adequately, this was overcome by adding 1 ml. of dextran intravenous solution. In general we do not recommend this, in view of a curious membrane which often forms when plasma, platelets, and dextran are incubated together.

Culture medium is prepared by adding phytohæmagglutinin ('Difco', not type M) 0·5 ml. and heparin 500 units to 100 ml. of T.C.199. If not already present, penicillin and streptomycin (to about tenfold the body concentration in therapeutic use) may be added. This is divided into one dozen culture vessels of about 20 ml. capacity, which have previously been filled with 5% CO_2 in air (not oxygen), and these are stored in a refrigerator or deep freeze until required. We use druggists' vials with a plastic snap top. These can be purchased in an almost sterile condition and sterilised by flaming the vial and rinsing the top in alcohol. Transfer of medium, and additions, are made by syringe.

If, intentionally or otherwise, less than 5 ml. of blood is drawn, the volume should be made up to 5 ml. by drawing AB serum into the syringe. We have found no impairment in this serum after several months' storage in a deep freeze, although repeated thawing and freezing should be avoided because fatty clumps tend to form. Sedimentation is often slower after dilution, with a less abrupt demarcation. For blood volumes of 0·5 to 1·5 ml. from children without acquired disease, the whole supernatant may be added without counting. Blood may be drawn from a heel stab directly into the hub of the syringe.

After ejection of the inoculum, the syringe is tilted to bring the interface of the sediment against the orifice, and blood-films with a high proportion of leucocytes are prepared for nuclear sexing. The syringe is then sealed and stored, needle upright, in a refrigerator; the next day the supernatant plasma is added to the culture. We preserve the red cells so that blood-grouping studies can be carried out if there is an appropriate chromosomal aberration.

The cultures are harvested 3–4 days later, after 2–6 hours' exposure to colchicine at 5×10^{-7} molar, according to the method described by Moorhead et al.[2] We have found no serious drawback in not washing the cells, adding water directly to the medium. Loss of cells by adhesion to pipettes may be prevented by dipping these in embedding wax. The standard hæmatological methods provide a satisfactory stain.

Now that the difficulties and expense of preparing slides are trivial compared to those of analysis, we feel that, whatever number of cells are analysed, for optimal discrimination at least some of these cells should be parental. In practice it is very much easier to acquire parental blood before the child's blood has been examined (on the grounds of comparison with the parental "norm") than after, when the parents are likely to suspect their own possible abnormality.

Various further simplifications are possible, but our experience is too limited for an unguarded recommendation. We have recently had excellent results from adding colchicine at implantation to a final concentration of 2×10^{-8} molar. This produces a greatly increased mitotic rate from which a larger number, although a smaller proportion, of intact cells with minimal contraction can be chosen for detailed analysis.

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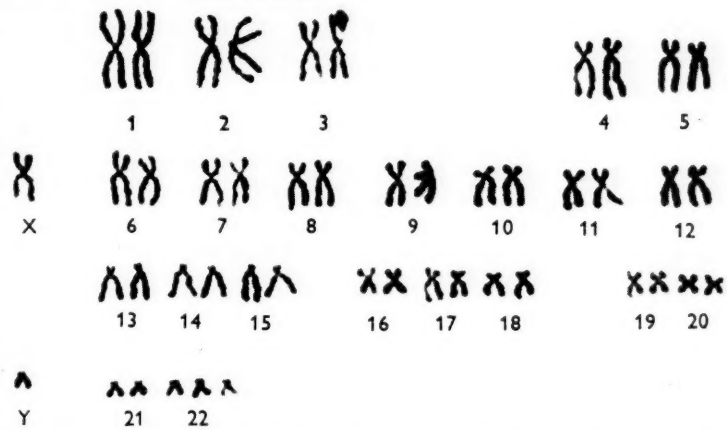
J. H. EDWARDS
R. B. YOUNG.

TRISOMY FOR CHROMOSOME 22

SIR,—Recent correspondence in *The Lancet* on the phenotypic expression of trisomy for chromosome 22 [1–5] prompts us to make a preliminary report of a case we are investigating.

An 8-year-old boy was admitted to our children's psychiatric unit because he was destructive, asocial, and defiant. He was of normal height and weight, with some facial anomalies, including a receding chin, flattened occiput, and wide nostrils. Because of myopia (right eye −12 dioptres and left eye −14 dioptres) he had worn glasses from the age of 8 months. Apart from some hyperextensibility of the elbows, no other physical abnormalities, and, in particular, stigmata of mongolism, were detected. On psychological testing, he is a schizophrenic child with dull-normal intelligence.



Chromosome analysis, by the method of Hungerford et al.[6] has shown, on two occasions, a chromosome number of forty-seven. Karyotypes show a trisomy for chromosome 21/22, which on satellite distribution appears to be 22 (see figure).

The mother's karyotype is normal; the father died of a cerebral tumour at the age of 33. Further studies on the family are proceeding.

Examination of another boy, with an almost identical facies, and myopia and autistic tendencies, showed, to our disappointment, a normal chromosome number and karyotype.

Hayward and Bower [1] suggested that trisomy for chromosome 22 might be associated with the Sturge-

1. Hayward, M. D., Bower, B. D. *Lancet*, 1960, ii, 944.
2. Lehmann, O., Forssman, H. *ibid.* p. 1450.
3. Hayward, M. D., Bower, B. D. *ibid.* 1961, i, 558.
4. Gustavson, K.-H., Höök, O. *ibid.* p. 560.
5. Hall, B. *ibid.*
6. Hungerford, D. A., Donnelly, A. J., Nowell, P. C., Beck, S. *Amer. J. hum. Genet.* 1959, **11**, 215.

Weber syndrome, but subsequent reports [2–5] have not confirmed their findings. It seems that, if a constant phenotype is to be related to trisomy of chromosome 22, this expression will be minimal compared with that of mongolism. Hayward and Bower [3] raised the possibility of the additional chromosome in their case being an isochromosome and having no genetic expression. These possibilities can only be resolved by phenotype analysis.

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BRIAN TURNER
A. N. JENNINGS.

DICHLORPHENAMIDE

SIR,—I have recently read [7–12] of the use of dichlorphenamide (' Daranide ') to treat severe chronic bronchitis and emphysema. Most of my patients live in industrial Warrington where chronic bronchitis and emphysema is an all too familiar problem. I decided to try dichlorphenamide in some of the most severely affected. The following are only clinical impressions. It would have been desirable to include measurements of pCO_2 and pO_2, in addition to direct measurements of ventilation, but these objective studies are not possible in general practice.

CASE 1.—Retired male nurse, aged 67. Bronchitis and emphysema for five years. Two coronary thromboses: poor prognosis. No sustained improvement: by the end of the year going to the lavatory produced severe tachycardia and dyspnœa. Aminophylline injections and oxygen required daily. Given 200 mg. of dichlorphenamide daily. Objective and subjective improvement within a week. Aminophylline and oxygen now seldom required. Continuous progress since; now leading a normal life for his age. Side-effects (first four weeks only): drowsiness and forgetfulness. Result: excellent.

CASE 2.—Man, aged 65. Emphysema and cor pulmonale. Confined to his house for twelve months. After a few days on dichlorphenamide breathing improved and pulse-rate slowed. When dichlorphenamide stopped for one week, condition deteriorated. No side-effects. Result: excellent.

CASE 3.—Man, aged 57. Severe chronic bronchitis and emphysema. Long absences from work in winter. After dichlorphenamide, much-improved exercise tolerance. Has worked regularly since. No side-effects. Result: excellent.

CASE 4.—Man, aged 70. Breathing much improved after three weeks on dichlorphenamide. No longer needs home visit. No side-effects. Result: excellent.

CASE 5.—Woman, aged 62. After three weeks reported no improvement. Side-effects: nausea and tingling in the fingers. Treatment stopped. Result: no benefit.

CASE 6.—Man, aged 58. Extensive emphysematous lung changes. Has not worked for over two years. 200 mg. dichlorphenamide daily caused drowsiness; dose reduced to 100 mg. daily. Breathing easier; now able to lie on his left side (impossible for past two years). Not sufficiently improved to return to work. Result: good.

CASE 7.—Man, aged 63. Emphysema. After one month no improvement. No side-effects. Result: poor.

CASE 8.—Man, aged 68. Longstanding emphysema and incipient cor pulmonale. Side-effects: paræsthesiæ of the fingers after three days on the drug. Treatment stopped. Result: poor.

CASE 9.—Man, aged 56. Discharged from the Army in 1946 on account of chest condition. Breathing was eased after one week. Improvement maintained. Side-effect: dizziness. Result: good.

CASE 10.—Man, aged 55. Grossly emphysematous. Much improved. No side-effects. Result: excellent.

7. *Lancet*, 1960, i, 1120.
8. *Idem*. *Ibid*. Jan. 7, 1961, p. 54.
9. Harris, L. E. *Ibid*. Feb. 18, 1961, p. 398.
10. Wahi, P., McCarthy, C. F. *Ibid*. March 18, 1961, p. 620.
11. McNicol, M. W., Pride, N. B. *Ibid*. April 29, 1961, p. 906.
12. Ahuja, M. T. *Ibid*. May 13, 1961, p. 1058.

Dichlorphenamide seems valuable in helping these unfortunate patients with severe emphysema to lead a more pleasant and useful life.

Appleton, Warrington,
Lancashire.

HAROLD W. K. THOMPSON.

CRIMES OF SEXUAL VIOLENCE

SIR,—The Wolfenden Committee reported in favour of an attempt to " clean up " street prostitution. The police and the courts have in practice gone considerably beyond this recommendation, and a recent Lords decision seems to pave the way for administrative action against any system by which prostitutes may privately acquire customers. The moral and psychological issues can, I know, be indefinitely debated, but there is one question of fact which would be worth clearing up.

It is widely believed by laymen, judging from comments made to me, that some recent crimes of sexual violence with paraphilic features—the Jones case in particular—are a direct consequence of this policy. It should be possible for someone to find out whether or not this is so; the answer would be instructive either way, and possibly the first instance of the profit which could accrue from the policy of studying pathological offenders rather than hanging them unstudied.

Loughton,
Essex.

ALEX COMFORT.

ATHEROMA IN THE BANTU

SIR,—We find ourselves completely at variance with the views of Dr. Laurie and Dr. Woods (April 1) which are a reiteration of their previously published work.[1] They deny the rarity of heart-disease due to coronary atherosclerosis in the Bantu and affirm that cryptogenic heart-disease in the Bantu " consists largely of undiagnosed cases of well-recognised causes of heart-disease, notably decompensated hypertension, pericardial disease, and coronary heart-disease ". These views differ radically from those of other South African workers [2–15] and, because of the importance of the subject we should like to examine critically the evidence [1] on which they are based.

The contention of Laurie et al. that heart-disease due to coronary atherosclerosis is not uncommon in the Bantu, was to a large extent based on subjective evidence—the occurrence of what they interpreted as angina pectoris. They did not state whether the symptom was volunteered or elicited, and they admitted that " less attention was paid to the quality of the pain as the descriptive powers of the Bantu are limited ". Yet, *excluding syphilitic cases*, they claimed that 24 (13%) of 186 consecutive Bantu patients with heart-disease suffered from angina pectoris. This is a remarkably high figure considering that nearly all these 186 patients were in congestive cardiac failure, in which state it is generally agreed that angina pectoris tends to become less severe or to disappear. Furthermore, other workers [9 16 17] ourselves included, agree that, except in syphilitic aortitis, angina is excessively rare in the Bantu. It is still more significant that in none of the 24 cases alleged to have

1. Laurie, W., Woods, J. D., Roach, G. *Amer. J. Cardiol.* 1960, **5**, 48.
2. Gillanders, A. D. *Brit. Heart J.* 1951, **13**, 177.
3. Becker, B. J. P., Chatgidakis, C. B., van Lingen, B. *Circulation*, 1953, **7**, 345.
4. Higginson, J., Isaacson, C., Simson, I. *Arch. Path.* 1960, **70**, 497.
5. *S. Afr. med. J.* 1957, **31**, 854.
6. Schwartz, M. B., Schamroth, L., Seftel, H. C. *Med. Proc.* 1958, **4**, 275.
7. Grusin, H. *Circulation*, 1957, **16**, 27.
8. Adams, E. B., Wainwright, J. *Brit. med. J.* 1958, **2**, 914.
9. Trowell, H. C. Noninfective Disease in Africa. London, 1960.
10. Becker, B. J. P. *S. Afr. J. med. Sci.* 1946, **11**, 97.
11. Higginson, J., Pepler, W. J. *J. clin. Invest.* 1954, **33**, 1366.
12. Schrire, V., Uys, C. J. *Amer. J. Cardiol.* 1958, **2**, 453.
13. Vogelpoel, L., Schrire, V. *Lancet*, 1955, ii, 1108.
14. Sacks, M. I. *Circulation*, 1960, **22**, 96.
15. Brock, J. F. Recent Advances in Human Nutrition. London, 1961.
16. Gelfand, M. The Sick African. Cape Town, 1957.
17. Schrire, V. *Amer. Heart J.* 1958, **56**, 280.

angina pectoris was there electrocardiographic confirmation in the form of the characteristic ST-segment depression; nor was any mention made of supportive evidence of coronary heart-disease such as U-wave inversion, sharp-angled ST-T junctions, the symmetry or otherwise of the T-wave changes, or the presence of post-extrasystolic T-wave changes. There are no reports of exercise tests or of the effects of amyl nitrite. They published no electrocardiograms; yet we are informed by Laurie et al. that electrocardiography was a routine examination.

We consider the premise of Laurie et al.—that small foci of myocardial fibrosis are minute infarcts due to coronary atherosclerosis—to be completely untenable. Patchy interstitial fibrosis is a frequent finding in the hearts of those dying of heart-failure due to a number of causes, including cryptogenic cardiomyopathy, without the coronary arteries being diseased. There is no doubt that atherosclerosis is found in the Bantu; but he rarely shows the more severe grades of calcification, ulceration, and hæmorrhage. This was clearly stated by Higginson and Pepler,[11] and more recent observations have confirmed this finding.[18] Even more striking perhaps is the extreme rarity of myocardial infarction. At this hospital with 2000 beds and serving 750,000 Bantu, and at which about 600 necropsies are performed on adults every year, on average only 1 case of myocardial infarction is seen each year.

Equally dubious is the evidence for the contention of Laurie et al. that cryptogenic cardiomyopathy in the Bantu consists largely of the triad of "decompensated hypertension", pericardial disease, and coronary heart-disease. Some of their notions of the latter condition have already been examined. "Decompensated hypertension" is the term Laurie et al. use to describe a group of Bantus with heart-disease admitted in heart-failure with normal blood-pressure levels "but with records of previous admissions for hypertensive cardiac failure". In our experience such an entity is rare, if indeed it occurs at all. In our view a minimum condition for substantiating this entity would be a detailed study of the behaviour of the blood-pressure both during and between all the previous episodes of heart-failure, mainly because the course of cryptogenic cardiomyopathy is characteristically punctuated by several episodes of heart-failure. In these the blood-pressure frequently rises, only to return to normal levels when failure subsides. This information Laurie et al. do not provide. Instead they state that the diagnosis of "decompensated hypertension" was substantiated by (a) electrocardiographic evidence of left ventricular hypertrophy and (b) "the appropriate renal changes". The former is fallacious since such evidence is commonly found in cases of cryptogenic cardiomyopathy; and the latter, without a description of the nature of the renal changes, is vague.

The evidence of pericardial disease, the remaining member of the triad held by Laurie et al. as largely accounting for cryptogenic cardiomyopathy, was based on the finding that, of 21 cases which they themselves diagnosed during life as cryptogenic heart-failure and which subsequently came to necropsy, 4 were shown by the pathologist to be cases of tuberculous or amœbic pericarditis. We acknowledge that the clinician may have difficulty in distinguishing cryptogenic cardiomyopathy from pericardial effusion, but we would stress that a careful clinical, electrocardiographic, and radiological examination will nearly always differentiate the two conditions. A 20% diagnostic error we would consider too high. These were not the only misdiagnoses in this group of 21 cases. A further 12 patients were found at necropsy to have nephrosclerosis (5 cases), aortic or mitral-valve disease (3 cases), myocardial infarction (2 cases), malignant hypertension (1 case), and syphilitic aortitis with ostial stenosis and myocardial infarction (1 case). But all were diagnosed clinically as cardiac failure of unknown cause. Yet Laurie and Woods suggest that other clinicians are "failing to recognise many examples of well-recognised causes of cardiac failure".

We wish emphatically to affirm that cryptogenic cardiomyopathy is a distinct and common entity in the Bantu. Its existence and frequency have been accepted by many workers, including Grusin,[7] Gillanders,[2] Higginson,[4] Wainwright,[8] Becker,[3] Davies,[5] and Trowell.[9] It is recognisable on clinical, electrocardiographic,[10] and pathological criteria, and should not be confused with any of the known causes of heart-disease. In individual patients coming to necropsy the pathological findings confirm the clinical diagnosis in most cases. That the necropsy incidence is lower than the clinical incidence may be explained by the fact that (a) a proportion of cases are reversible,[20 21] and (b) follow-up studies are revealing that many patients die at home.

These criticisms are by no means exhaustive. We hope, however, that they will go some way to correcting what we believe to be a distorted view of heart-disease in the South African Bantu.

The remarks of Dr. Laurie and Dr. Woods should not be allowed to obscure the different incidences of various diseases in Bantu and whites—differences which probably have an environmental rather than a racial basis.

C. ISAACSON
H. C. SEFTEL
L. SCHAMROTH
K. J. KEELEY.

South African Institute for Medical Research and Baragwanath Hospital, Johannesburg.

18. Reef, H., Isaacson, C. To be published.

AUTOIMMUNITY IN ULCERATIVE COLITIS

SIR,—The pathogenesis of ulcerative colitis, in spite of much investigation, still remains conjectural; there are reasons for believing that immunological mechanisms may be involved.

The association of ulcerative colitis with recognised hypersensitivity disease such as arthritis[22 23] conjunctivitis,[24] erythema nodosum, pyoderma gangrenosum, and lupus erythematosus[25] is well documented; and the incidence of drug and transfusion reactions is high in this condition. While the microscopic picture is not pathognomonic of allergy, the infiltration by lymphocytes, eosinophils, and plasma cells, the vascular congestion, stasis, and thrombosis, and the occurrence of granulomata would all fit such a hypothesis. The allergic theory is not entirely satisfactory, however, because a direct association between the disease and a specific antigen has never been observed, and the disease has not been produced experimentally by immunological methods.

Recently, autoimmunity has been invoked as the particular immunological mechanism concerned in this disease process. Broberger and Perlmann,[26] Asherson and Broberger[27] and Polcak[28] reported finding circulating antibodies to an extract of human colon in the sera of patients with ulcerative colitis.

We have failed to demonstrate antibodies to human colon extracts in the sera of 50 patients with ulcerative colitis.

Antigen.—Human colonic mucosa was obtained fresh from fœtal colons and from colons removed from adults with carcinoma or ulcerative colitis; it was stored at −20°C if an extract could not be prepared immediately (extracts were made from twelve different colons, most of which had been stored at −20°C). Initially they were extracted with saline, but most antigen preparations were extracted with phenol-water.[29]

Tests.—Examination for precipitins was carried out on gel-diffusion plates in 1% agar phosphate buffered saline. The more sensitive tanned-red-cell hæmagglutination test[30] (T.R.C.H.) for antibodies was also performed, using the same technique as Broberger and Perlmann.[26] The sera were serially diluted, 1/2 up to 1/256 in the agar, and up to 1/1024 for the T.R.C.H.

Specimens.—Sera from 50 patients with ulcerative colitis were examined as above for antibodies against the human colonic-mucosa

19. Schamroth, L., Blumsohn, D. *Brit. Heart J.* (in the press).
20. Keeley, K. J. *S. Afr. med. J.* 1960, **34**, 1072.
21. Seftel, H. C., Susser, M. *Brit. Heart J.* 1961, **23**, 43.
22. Brooke, B. N. Ulcerative Colitis and its Surgical Treatment; p. 65. Edinburgh, 1954.
23. Sloan, W. P., Bargen, J. A., Gage, R. P. *Gastroenterology*, 1950, **16**, 25.
24. Crohn, B. B. *Amer. J. med. Sci.* 1925, **169**, 260.
25. Ricketts, W. E., Benditt, E., Palmer, W. L. *Gastroenterology*, 1945, **5**, 272.
26. Broberger, O., Perlmann, P. *J. exp. Med.* 1959, **110**, 657.
27. Asherson, G. L., Broberger, O. *Brit. med. J.* 1961, i, 1429.
28. Polcak, J., Vokurka, V. *Amer. J. dig. Dis.* 1960, **5**, 395.
29. Westphal, O., Luderity, O., Bister, F. *Z. Naturf.* 1952, **7B**, 148.
30. Boyden, S. V. *J. exp. Med.* 1951, **93**, 107.

extracts. There were 29 women and 21 men in this group, and their ages ranged from 16 to 57 years. 27 of them required surgical treatment.

The sera produced no precipitin lines in agar with any of the extracts. Some positive results were observed in the T.R.C.H., but in every such case either the controls were not satisfactory or the results could not be reproduced.

We would be interested to know if others have had the same experience.

This work has been carried out in the departments of experimental pathology and surgery, Birmingham Medical School, and the department of bacteriology, Glasgow Royal Infirmary; and the protocol of the experiment is deposited in the medical school library, Birmingham University.

We wish to thank Prof. P. G. H. Gell for his guidance and Mr. B. N. Brooke and Dr. C. Hawkins of the Queen Elizabeth Hospital, Birmingham, for sera from their patients.

We are grateful to the M.R.C. for a personal grant to one of us (J. G. G.).

J. G. GRAY
F. C. WALKER
D. THOMPSON.

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WHAT MAKES THE PATIENT BETTER?

SIR,—Dr. Meares (June 10) raises a fascinating question. What he describes would seem to be explicable by the hypothesis that there can be direct communication between one unconscious mind and another. In the case of the Yogi, it is easy to see how this would work: with the patient who unaccountably got better, it might be more difficult to imagine the process. However, to describe it in a very simplified way, it might be something like this:

A woman comes to a psychiatrist with a headache. She (unconsciously) feels guilty, say, about her mother's death. Being a psychiatrist, the doctor can "see through her", she believes; whatever, and however little she told him, he would still know the truth about her. Now he has given her no indication, after one or more interviews, that he thinks her wicked, so she cannot be. She need therefore not have the headache, which was an expiation, any longer.

This kind of process would, of course, be going on in the patient's subconscious mind. Would it be too far-fetched, to imagine that it might be more therapeutic than a superficial form of insight, a mere verbalisation, given to the patient? And is there any reason to believe that the unconscious basis of a mental state can only be modified by conscious insight?

Why not postulate a short cut between the unconscious of two people? This might operate in "intuition", as well as in psychotherapy.

London, N.8. R. L. S. CHAZAN.

COMPENSATION FOR CUPIDITY?

SIR,—The letters of Dr. Miller (June 17) and Dr. Howard (June 3) are interesting but their suggested remedies cumbersome.

Industrial neurosis and "compensationitis" do not arise in an injured workman who is enabled to remain at work, without break and at the same place of work. To achieve this, there must be an industrial medical officer to treat the injury within the factory and to arrange temporary and graduated employment from the time of the accident until full recovery, or permanent transfer to another job if this is necessary.

True, some injuries necessitate absence from work and surgical treatment, but they are a very small proportion of the whole—about 0·1%—and their return to work is also speeded and facilitated by the existence and liaison of an industrial medical officer. But there are too many places of employment without the services of an industrial medical officer.

The remedy is for the State to provide a financial incentive to employers to employ industrial medical officers. This could take the form of a percentage rebate on their weekly expenditure on National Insurance stamps, allowed when there has been set up an approved industrial medical service with a medical officer, full or part-time depending on the size of the firm.

Oxford. W. A. REYNARD.

RESTITUTION OF INTERNAL CAROTID ARTERY

SIR,—I have read with interest your annotation (April 15) and the letter by Mr. Taylor (April 29). The generally poor prognosis of occlusion of the internal carotid artery leads me to report the following case:

A 49-year-old electrician fell through a roof on to the concrete floor below at 8 P.M. on the evening of April 2, 1961. His neck was struck a glancing blow on a projecting object as he fell, and the back of his head hit the floor He lost consciousness for approximately ten minutes and was admitted to the local district hospital where no neurological abnormalities were noted on examination. Next morning he complained of headache; and weakness of the left arm, progressing rapidly to total paralysis, was noted, though consciousness was not impaired. The left leg too was weak. He was transferred to the Royal Perth Hospital with a diagnosis of right-sided subdural hæmatoma. I confirmed the previous neurological findings, and requested carotid angiography. The report read:

"*Arteriogram.*—The right common carotid artery was punctured and, despite good back-flow, no contrast medium passed into the cranium and only the external carotid vessels and their branches were outlined. A film of the neck revealed a complete block of the internal carotid artery approximately 1 cm. from its origin.

"The left common carotid artery was then injected and satisfactory anteroposterior films obtained. Spontaneous cross-filling of the opposite anterior cerebral artery, and part of the middle cerebral artery, occurred. The anterior cerebral vessels lay in the midline and there was no evidence of any abnormal displacement of the vessels outlined.

"Reviewing the external carotid arteriogram on the right side, there is no evidence of any collateral circulation filling the branches of the internal carotid system on the right side and the findings would be consistent with a recent occlusion of the right internal carotid artery near its origin."

Exploration of the right carotid bifurcation was undertaken at 8 P.M. on April 3, 1961, approximately twenty-four fours after injury. The tissue planes of the neck and the carotid vessels showed no evidence of recent bruising. The internal carotid vessel was pulseless, and on palpation the bifurcation was found occupied by a firm thrombus. Arteriotomy displayed a bean-shaped organised thrombus completely occluding the internal carotid lumen in its proximal 2 cm. It separated readily from the intima of the vessel, and its removal re-established pulsatile flow in the proximal portion of the vessel. The distal portion of the vessel showed no retrograde flow, but after passage of a fine polyethylene tube to the base of the skull, and gentle irrigation with heparin solution, retrograde flow recommenced and increased to a steady but non-pulsatile flow within a few minutes. An atherosclerotic plaque was observed at the site of thrombosis and the arteriotomy incision was extended proximally to see better. The distal centimetre of the common carotid, and the proximal 2 cm. of the internal carotid vessel were occupied by an atherosclerotic ring and the orifice of the external carotid artery was also involved. Endarterectomy was undertaken and the vessels resutured. On releasing the clamps, vigorous pulsation as far as the base of the skull was felt in the right internal carotid vessel.

Anticoagulant therapy was continued postoperatively; a complication was a wound hæmatoma causing Horner's syndrome and right recurrent laryngeal paresis, but these are expected to disappear. Some return of power in the left arm was observed within twenty-four hours of operation and has progressed in the ensuing weeks to complete functional recovery. The left leg has also regained full power. Postoperative angiography has not been performed and there seems no reason to doubt that the right internal carotid vessel has remained open.

The case belongs to the first of the three groups

described by Riishede et al.[1] and cited in your annotation. It is of interest because undoubtedly thrombosis was precipitated by indirect trauma in a patient who had suffered no previous transient hemiparesis, but who had an atherosclerotic plaque, injury to which during the fall presumably inititated thrombosis which progressed to complete occlusion of the internal carotid vessel.

Early exploration and re-establishment of back-flow were undoubtedly major factors contributing to the successful outcome. The case lends timely support to the plea made by Taylor for a more constructive approach to the problem of internal-carotid-artery occlusion. The possibility of embolism at operation will not contra-indicate exploration in cases of *hemiplegia* due to carotid thrombosis, and back-flow may at times be re-established in recent cases. A bigger problem is to have cases of recent complete occlusion referred to a neurosurgical department soon enough for surgical treatment to succeed. In cases of " stuttering " type, it would appear reasonable to plan deliberately for urgent neurosurgical investigation and treatment of any episode causing severe symptoms lasting more than 6 hours.

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CHLORHEXIDINE AND *Proteus rettgeri* INFECTION

SIR,—In their preliminary communication of April 29, Dr. Lubsen and his colleagues concluded that chlorhexidine should no longer be used in urology. I would like to make the following comments.

The inhibitory values which they cite for gram-negative and gram-positive bacteria are approximately 5 times lower than those obtained by myself [2] and by other workers.

We have recently investigated 16 strains of *Proteus rettgeri*, 8 of which were from the National Collection of Type Cultures, London, and 8 from the National Institute for Public Health, Utrecht. The medium used was 10 ml. of 1% glucose-broth (Liebig's meat extract with 'Bactopeptone,' 0·5% NaCl, pH≃7·6), and the inoculum was 0·1 ml. 1/1000 24-hour broth culture (approximately 10^{10} bacteria per tube). After 24 hours at 37°C, 0·5 ml. was inoculated on 20% egg-yolk agar. 9 strains showed no growth at 1/50,000, and 7 no growth at 1/10,000 chlorhexidine. Further, approximately 10^{15} bacteria of a strain which was inhibited at 1/10,000 were inoculated on to broth-agar containing 1/1000 and 1/5000 chlorhexidine in Roux bottles. After 4 days of incubation at 37°C no colonies were observed.

At my request Dr. Lubsen kindly sent me 3 proteus strains: 1 *Pr. rettgeri* which in Dr. Lubsen's laboratory had shown no growth after 24 hours at 1/8000 and after 48 hours at 1/4000, and 2 *Pr. mirabilis* strains which had shown no growth after 24 hours at 1/4000 and after 48 hours at 1/2000 after inoculation on blood-agar. Inoculations were made from a 1/1000 broth-culture. With chlorhexidine digluconate (20% concentrate), and 1% glucose-broth as medium, we obtained the following results from inoculation of approximately 10^7 bacteria (Lubsen's figures are shown in parentheses):

Pr. rettgeri	after 24 hours	1/20,000:	no growth	(1/8000)
	,, 48 ,,	1/20,000:	,, ,,	(1/4000)
Pr. mirabilis I	,, 24 ,,	1/10,000:	,, ,,	(1/4000)
	,, 48 ,,	1/10,000:	,, ,,	(1/2000)
Pr. mirabilis II	,, 24 ,,	1/10,000:	,, ,,	(1/4000)
	,, 48 ,,	1/10,000:	,, ,,	(1/2000)

From comparison of the figures it appears that Lubsen's findings are $2^1/_2$–5 times lower than mine. When the experiment was repeated, with an inoculum of 10^{10} organisms per tube, the same results were obtained. These experiments show that the lowest bactericidal concentration for *Pr. rettgeri* and some *Pr. mirabilis* strains is 1/10,000, even for the strains obtained from Dr. Lubsen. I wonder whether Lubsen et al., when making the dilutions, realised they were working with a 20% concentrate.

As proof that using chlorhexidine was the reason for the increase of proteus infections, Lubsen et al. mention the more frequent isolation of *Pr. rettgeri* since 1957, when chlorhexidine was introduced into their clinic. This may have been a coincidence. Every urologist knows that clinical urinary infections can be due to several causes. The concentrations 1/5000–1/10,000 chlorhexidine as used for bladder irrigation are only of prophylactic value. The solution must not contain commensals or pathogens. If chlorhexidine in a solution 1/10,000 is bactericidal to 10^{10} bacteria under the conditions described above, it is no doubt justifiable to use this antiseptic as an irrigation in a properly prepared solution. Lubsen et al. speak of 15 *Pr. rettgeri* strains. Is there evidence that they actually investigated 15 different strains rather than, say, 5 times 3 strains of different antigenic structure? In this respect one only needs to think of the staphylococcal hospital infections.

In conclusion, I think that, although proteus strains may be less sensitive than other bacteria to chlorhexidine, there is no reason for not using chlorhexidine just because the bactericidal concentrations are 1/10,000 or more, whereas the concentrations used for bladder-irrigation are 1/5000 or 1/10,000.

St. Joseph Ziekenhuis,
Heerlen,
The Netherlands. H. BEEUWKES.

*** This letter has been shown to Dr. Lubsen and his colleagues, whose reply follows.—ED. L.

SIR,—We should like to answer the criticisms put forward by Dr. Stewart and his colleagues (May 13), by Dr. Gillespie and his colleagues (June 10), and by Dr. Beeuwkes.

After reading Dr. Beeuwkes' letter we recorded growth (*a*) in 1% glucose-broth medium at pH 7·6 prepared according to his formula, (*b*) in tryptose-phosphate broth ('Difco') at pH 7·3 (the medium used in our previous investigation), and (*c*) in urine at pH 7·3. The growth of the two strains of *Proteus mirabilis*, which we sent to Dr. Beeuwkes, and of a strain of *Escherichia coli* were compared. All tests were carried out in duplicate as described in our preliminary communication, and were repeated. The dilutions of chlorhexidine digluconate were simultaneously prepared. The inoculum contained approximately 500,000 bacteria. During these experiments we confirmed both Dr. Beeuwkes' results and our own (see accompanying table). In urine at pH 7·3 as a culture-medium, bacteria grew at intermediate concentrations.

GROWTH OF ORGANISMS WITH CHLORHEXIDINE IN MEDIA

Medium	Two strains of *Pr. mirabilis*		One strain of *Esch. coli*	
	Highest concentration of chlorhexidine with growth	Lowest concentration of chlorhexidine without growth	Highest concentration of chlorhexidine with growth	Lowest concentration of chlorhexidine without growth
Tryptose broth	1/4000	1/2000	1/256,000	1/128,000
Glucose broth . .	1/16,000	1/8000	1/512,000	1/256,000
Urine	1/8000	1/4000	1/256,000	1/128,000

It appears that the difference between his results and ours is due to difference in broth media. As the inhibitory concentrations for *Esch. coli* reported by Dr. Beeuwkes [1] are lower than those reported by other investigators [2–4] or by ourselves, 1% glucose broth is apparently a poor medium for studying sensitivity of bacteria to chlorhexidine. Though translation from in-vitro work to clinical application is always difficult, it is clear that for in-vitro work the best media should be used.

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2. Beeuwkes, H. *Leeuwenhoek ned. Tijdschr.* 1958, **17**, 49.
1. Beeuwkes, H. *Leeuwenhoek ned. Tijdschr.* 1958, **24**, 49.
2. Davies, G. E., Francis, J., Martin, A. R., Rose, F. L., Swain, G. *Brit. J. Pharmacol.* 1954, **9**, 192.
3. Calman, R. M., Murray, J. *Brit. med. J.* 1956, ii, 200.
4. Paterson, M. L., Barr, W., Macdonald, S. *J. Obstet. Gynæc. Brit. Commonw.* 1960, **67**, 394.

When Dr. Beeuwkes uses a poor medium and finds that all bacteria are killed in that medium by a 1/10,000 concentration of chlorhexidine, he is not justified in stating that this concentration of chlorhexidine is adequate for bladder irrigation.

In our opinion Dr. Beeuwkes confirms some of our results. Further, in his experiments the sensitivity of *Pr. rettgeri* and *Pr. mirabilis* to chlorhexidine is much less (1/10,000 to 1/50,000) than the sensitivity of *Esch. coli* (1/1,000,000) he found earlier.[1] It can also be concluded from his work that we did not examine only chlorhexidine-resistant hospital strains. The sensitivity of our *Pr. rettgeri* strains and of the *Pr. rettgeri* strains from the National Collection of Type Cultures, London, appeared to be the same in his experiments.

Dr. Stewart states that " there is no evidence that resistance to chlorhexidine has developed ". We agree with this statement. Some of our strains of *Pr. mirabilis* insensitive to chlorhexidine were cultured from the urine of patients not treated in hospital.

Dr. Stewart questions our statement that " the growth of *Pr. rettgeri* is not inhibited by the concentration of chlorhexidine (' Hibitane ') used in our urological ward (i.e., 1/5000)", since " for 11 of 15 strains of *Pr. rettgeri* tested, the minimum bactericidal concentration of chlorhexidine was 1/8000 or less ". In a short contact test the effective dilution of antiseptics is much lower than in a 48-hour test.[3] According to an I.C.I. report [5] chlorhexidine kills 99·99% of *Esch. coli* bacteria in 10 minutes at double (i.e., 1/50,000) the minimum concentration inhibiting growth of *Esch. coli* after 24 hours (i.e., 1/100,000).[2] Our interpretation is that bladder irrigation with 1/5000 solution would be insufficient to kill organisms in a short time when the minimum bactericidal concentration for these organisms after 48 hours is 1/8000.

We completely agree with Dr. Stewart " that many factors contribute to the occurrence of infections in genitourinary wards ". Which of the control measures in urological wards contributes most to the important decrease in the infection-rate of the urinary tract is difficult to say. In introducing chlorhexidine in urology, Beeuwkes and de Vries [6] advised different uses of chlorhexidine and noted a significant decrease in urinary infections. Besides rinsing the bladder with a chlorhexidine solution, they simultaneously introduced a chlorhexidine cream for the staff to rub into their hands several times a day. The decrease in infection-rate in their ward might also be explained by the use of this antiseptic cream.

In our previous communication we did not mention that a 1/8000 concentration of chlorhexidine is insufficient to kill *Pr. mirabilis* in 48 hr. (see table). In broth, one of our strains of *Pr. mirabilis* grew scantily, and three strains of providencia (*Pr. inconstans*), recently isolated from urine, grew well at a concentration of 1/2000.

In conclusion, we must emphasise that proteus causes the most serious infections of the urinary tract: the urine becomes alkaline and stones may be formed. In some of our patients with *Pr. rettgeri* infections severe pyelonephritis could not be prevented despite intensive antibiotic treatment. Most proteus infections are hospital infections. The effect of chlorhexidine on proteus is inadequate as the concentrations of chlorhexidine necessary for inhibiting the growth of proteus are too toxic for the bladder mucosa. Experience in our hospitals indicates that the general use of chlorhexidine may produce a reservoir of *Pr. rettgeri* which will increase the cross-infection due to this species. The results of the scheme to prevent urinary infections, adopted by Dr. Gillespie and his colleagues, are certainly impressive. But in their scheme chlorhexidine is only used, together with mercury oxycyanide or 70% alcohol, for disinfecting cystoscopes and resectoscopes and for disinfecting the urethra. For general use, however, an antiseptic solution with insufficient effect on the most serious hospital infections of the urinary tract is, in the light of our experience, useless and perhaps even dangerous.

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Binnengasthuis, Amsterdam,
The Netherlands.

N. LUBSEN
W. BOISSEVAIN
HANNA FASS.

5. I.C.I. report. Cited by H. Beeuwkes (footnote 2).
6. Beeuwkes, H., de Vries, H. R. *Lancet*, 1956, ii, 913.

LABELLING OF MEDICINES

SIR,—I read with sympathetic interest the letters of Dr. Steer and Dr. Morrow Brown (June 10). I have had the same experience with local chemists. Most of my instructions to label boxes are ignored. Perhaps the following method, successfully adopted against drug firms to stop their flow of advertising material, could be used.

Any unlabelled box of pills should be *posted* back to the chemist concerned in an *unstamped* package, marked " urgent and confidential ", and with a circular enclosed asking the chemist to comply with the printed instructions on your prescription. The financial loss to the chemists concerned (postage-due fees, &c.) would soon make them label your tablet packages.

Hessle,
East Yorkshire.

ALLAN B. FIELDSEND.

DRUG ADDICTION

SIR,—I was most interested in your comments on drug addiction (May 27). I had never encountered a case until I began to work in the psychiatric emergency unit in Brighton. In the five months from January to May, 1961, 3·2% of a total of 124 male admissions and 5·5% of a total of 181 female admissions were drug addicts. These were 3 men and 6 women (some were admitted more than once).

Only 1 of my patients was addicted to a dangerous drug (pethidine), at least 1 to dexamphetamine, 1 to ' Drinamyl ', and the rest to barbiturates. The dexamphetamine addict also took quinalbarbitone. 2 of the patients were addicted to alcohol as well (the drinamyl addict and the dexamphetamine-quinalbarbitone addict).

None of the patients obtained supplies by a regular prescription from a general practitioner, though he was, in most cases, aware of the addiction. They usually had no difficulty in obtaining the drugs from their chemist. The pethidine addict bought his supplies through " contacts ". This was of course expensive, and when things became difficult he would somehow get himself into hospital, often by a " motivated " accident, presenting, if necesary, a faked and unsigned certificate stating that he was a drug addict and required 100 mg. pethidine four-hourly (he did).

Only the pethidine addict behaved in the classical way, requiring increasing doses which had less and less effect. The others would take more or less the same dose for years, but would increase it at times of stress, which usually led to confusion and hospital admisson. Others, it appeared, took drugs in bouts, like drinkers.

A young woman presented as a paranoid psychosis, and was at first diagnosed as such, though her garrulous confiding manner was quite out of keeping with schizophrenia. Her husband later revealed that she had long been addicted to drinamyl.

Only 2 patients had ever sought treatment for their addiction; another was undergoing group therapy for her neurosis and thus, one hoped, also for her addiction. None, of course, was registered as a drug addict. The pethidine addict had to state the dose he took in order to get it, but the others were extremely secretive about their drug-taking. Often they swore that they had given it up. Even their closest relatives could often only guess, in the spasmodic addicts, whether they had taken a dose.

These facts would suggest that there may be more drug addicts than we think.

London, N.8.

R. L. S. CHAZAN.

CRISIS IN HOSPITAL PHARMACY

SIR,—We thank you for your annotation of June 17. What you said applies equally to laboratory technicians and radiographers—that these services are understaffed and attract insufficient permanent career entrants, but are running on the older men and short-term female staff. Dissatisfaction is not only with rates of pay but with the interminable protraction of negotiations. At this moment technicians are awaiting action on an official report which was completed in January last. The prospect of another inquiry therefore fills us and them with dismay, because, much as we should like to see the negotiating machinery speeded up, the facts of this case are already known, and we fear that it may be yet another source of delay.

County Laboratory, Dorchester.

T. V. COOPER
A. N. BLADES.

PSEUDOTUMOR CEREBRI

SIR,—Reading your annotation of June 10, we were surprised that while the role of endocrine factors in the pathogenesis was stressed and attention was drawn to the association with menstruation,[1] Addison's disease,[2–4] and the response to methyl prednisolone in some cases,[5] no mention at all was made of the group of patients who have developed "pseudotumor cerebri" after therapy with steroids for several months.[6–16]

The observation [5] that five out of six patients with "pseudotumor cerebri" improved rapidly on methyl prednisolone is of special interest since in the majority (9 out of 14) of fully described cases [7–12 15] induced by steroids, symptoms developed shortly after the dose had been reduced. After increasing the dose again,[7 8 15] four out of five improved rapidly and the fifth more slowly. Evidence of adrenocortical or pituitary hypofunction in these patients included diminished urinary excretion of 17-keto and 17-hydroxy steroids,[7 15] retarded osseous development,[7 11] and low serum-sodium.[7]

We wish to report two more patients who developed "pseudotumor cerebri" whilst on long-term therapy with steroids. In one, onset of symptoms coincided with reduction of dosage, but rapid improvement occurred in both when the dose was increased.

CASE 1.—A boy aged 4 years and 4 months was found to have the nephrotic syndrome at 2 years and 6 months. There was gross subcutaneous œdema with ascites. The fundi were normal and the blood-pressure 120/90 mm. Hg. The urine contained albumin ++++. Total serum-proteins 4·5 (albumin 1·3, globulin 3·2) g. per 100 ml., cholesterol 303 and 473 mg. per 100 ml., electrolytes and blood-urea normal. He was treated with cortisone 50 mg. a day for 18 days only, and went into a clinical and biochemical remission. There was a transient relapse during an attack of measles three months later.

At 3 years and 3 months of age he was readmitted with acute pneumococcal peritonitis and a relapse of the nephrotic syndrome. He was treated with intramuscular penicillin and oral prednisolone 20 mg. daily. There was prompt recovery and a remission from the nephrotic syndrome. The dose of prednisolone was diminished to 5 mg. daily over 5 weeks and remained from 5 to 13·5 mg. daily until at 3 years and 7 months he developed sonne dysentery and a further relapse of the nephrotic syndrome. He was treated successfully with sulphasuccidine, sulphadimidine, and streptomycin. The dose of prednisolone was increased to 90 mg. daily and the patient again went into remission.

The dose of prednisolone was gradually diminished to 2·5 mg. daily over $7^1/_2$ months. Two days after reduction of prednisolone dosage from 5·0 to 2·5 mg. daily he began to vomit persistently. On examination, apart from the resemblance to patients with Cushing's syndrome and the small stature (height and weight less than the third percentile), the only abnormality was bilateral papillœdema, the blood-pressure being 110/85. There was no clinical or biochemical evidence of the nephrotic syndrome. Skull X-rays and E.E.G. were normal.

Vomiting ceased immediately the dose of prednisolone was increased to 5 mg. daily. The dose of prednisolone has since been gradually diminished. There was slight vomiting two weeks after the initial attack, but the papillœdema has slowly diminished.

CASE 2.—A boy aged 10 years and 2 months had recurrent attacks of bronchial asthma from 2 months of age. Attacks continued in spite of various forms of therapy. At 7 years and 6 months of age, in July, 1958, treatment began with prednisolone 5 mg. twice daily and penicillin V 120 mg. twice or three times daily. The dose of prednisolone was reduced to 2·5 mg. twice daily after five days, and continued with minor variations until November, 1959, when it was increased to 5·0 mg. twice daily. This dose was administered until May, 1960, when it was reduced to 2·5 mg. in the morning and 5·0 mg. at night. Six months later early papillœdema was detected but there was no headache or vomiting. The dose of prednisolone was not altered. No definite change was noted till February, 1961, when he complained of headache, vomiting, and blurred vision for the first time. At this time there was definite papillœdema. Apart from the resemblance to patients with Cushing's syndrome, no abnormality was noted on examination, his blood-pressure being 120/80. Skull X-ray and E.E.G. were normal. The dose of prednisolone was increased to 5 mg. three times a day. His symptoms stopped immediately and papillœdema slowly disappeared.

In all reported patients, steroids had been administered for at least five months. All except two (aged 16 and 40 years) had been under 10 years of age.

Earlier reports suggested that "benign intracranial hypertension" (pseudotumor cerebri) was a toxic effect of triamcinolone,[6 9 14] but of 21 cases, including those described in this letter, only 12 [6 7 9 12–16] had received triamcinolone. Moreover, in one of these, symptoms occurred when the daily dose of triamcinolone was reduced from 2 mg. to 1 mg. and symptoms disappeared when the higher dose was restored; and in the four patients described by Green et al.[16] the dose of triamcinolone may have been smaller than the equivalent of cortisone, suggesting that reduction of dosage was the precipitating cause. It is not clear how adrenocortical or pituitary hypofunction could be operative in patients in whom there had been no recent reduction in steroid dosage, as in our case 2. It is possible, however, that a relative insufficiency may have been provoked by an increase in steroid requirements as occurs, for example, during infections.

The indications for steroid therapy in patients who developed "pseudotumor cerebri" have been nephrosis,[6] asthma,[7 9–12] eczema, [7 10–12] polyarthritis,[8 14 15] osteitis,[15] psoriasis,[13] and the adrenogenital syndrome.[16]

We think that the recognition of steroid-induced "pseudotumor cerebri" is important, firstly to save

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4. Jefferson, A. *J. Neurol. Psychiat.* 1956, **19**, 21.
5. Paterson, R., De Pasquale, N., Mann, S. *Medicine, Baltimore*, 1961, **40**, 85.
6. Valentine, G. H. *Lancet*, 1959, i, 892.
7. Dees, S. C., McKay, H. W., Jr. *Pediatrics*, **23**, 1143.
8. Gaisford, W. *J. Pediat.* 1960, **56**, 259.
9. Laurance, B. M., Matthews, W. B., Shephard, R. H. *Lancet*, 1960, i, 701.
10. Benson, P. F., Pharoah, P. O. D. *ibid*, p. 1250.
11. Benson, P. F., Pharoah, P. O. D. *Guy's Hosp. Rep.* 1960, **109**, 212.
12. Warin, R. P., Evans, C. D. *Lancet*, 1960, ii, 42.
13. Sneddon, I. B. *ibid.*
14. Jolly, H. *ibid.*
15. Royer, P., Vermeil, G., *Méd. Hyg.* 1961, no. 492, 159.
16. Green, O. C., Cleveland, W. W., Wilkins, L. *Pediatrics*, 961, 2, 292.

patients uncomfortable and unnecessary investigations, such as air encephalography and cerebral angiography: and secondly because further study of this condition may help to throw more light on the mechanism of "pseudotumor cerebri".

Guy's Hospital, London, S.E.1.

PHILIP F. BENSON
RONALD C. MAC KEITH.

THE APLASTIC CRISIS IN SICKLE-CELL ANÆMIA

SIR,—Dr. MacIver and Dr. Parker-Williams (May 20) accept only two types of crisis in sickle-cell anæmia—the clinical or painful crisis, and the aplastic or hæmatological crisis.

We have noted, however, a pure hæmolytic crisis with all the clinical and laboratory findings, in many cases of sickle-cell anæmia in this clinic. Two patients died during this hæmolytic crisis.

On the other hand, the authors do not speak about the maturation arrest of the erythroblastic series, which accompanies indispensably the erythroblastopenia, as described by Owren and Gasser. Recently Cazal et al.,[1] who have studied the erythroblastic series by karyometry, have described in detail this maturation arrest. We have also studied by karyometry this "aplastic crisis" in 10 patients with different types of hæmolytic anæmia, and we have definitely found in all cases the complete maturation arrest. The erythroblastic series was not always hypoplastic, but sometimes hyperplastic.

We do not believe that cases 6 and 7, described by MacIver and Parker-Williams, show either an erythroblastopenia or a maturation arrest. We think, too, that the reticulocyte-count in the blood is not sufficiently low, because, in all our cases, we found a reticulocyte count of nearly zero. In case 8 no bone-marrow examination was done. On the other hand, the reticulocyte count was increased.

Thus we believe that the so-called "aplastic crisis" is not so common during the evolution of the hæmolytic anæmia, but that it is a rather rare phenomenon.

2nd Medical Clinic, University of Athens.

H. TSEVRENIS
A. PAPASPYROU
N. VORIAS.

ANTEPARTUM HÆMORRHAGE AND THROMBOSIS OF PARAMETRIAL VEINS

SIR,—A young woman aged 27 was admitted to my department as an emergency. She was in the fourth to fifth month of pregnancy and had acute and severe uterine bleeding.

I had immediately to remove the necrotic fœtus and the placenta, and perform a curettage under thiopentone anæsthesia. 'Pituitrin' and ergometrine were given, and the uterus was massaged; but it did not contract. She continued to bleed profusely, and became shocked, despite blood and plasma transfusions. A supravaginal amputation of the uterus had to be carried out.

While cutting through the parametrial veins I observed that their cut ends were obliterated by thrombi. I therefore unclamped all these veins and found them filled with soft thrombi, 10–12 cm. long, which could easily be extracted with simple forceps. The postoperative course was normal, and she recovered without complications.

The following questions arise:

(1) Is bleeding from the uterine cavity caused by a primary thrombosis of the parametrial veins, so that the blood cannot take its normal course through them, and consequently flows out of the uterine cavity?

(2) Do the lack of contractions of the uterine musculature cause uterine bleeding and stasis with consequent thrombosis of the parametrial veins due to the absence of "*vis a tergo*"?

(3) Is there a neurogenic factor which causes shock and the heavy bleeding and maybe even thrombosis of the parametrial veins?

I should like to know whether others have observed similar thrombosis of the parametrial veins when they have amputated the uterus because of heavy uterine bleeding.

Shaare Zedek Hospital, Jerusalem, Israel.

W. OPPENHEIMER.

FAILURE TO DEMONSTRATE ANTIBODY TO SPERM IN SERUM OF PROSTITUTES

SIR,—Rümke and Hellinga[1] recently demonstrated by an agglutination method antibody to sperm in the serum of about 3% of husbands in childless marriages. Such immunisation has been thought to be a cause of infertility in prostitutes[2 3] but, to our knowledge, no specific investigations have been reported. Because a simple method of demonstrating antibody to sperm would be valuable in studying childless marriages, we tried out the Coons labelled-antibody technique with this in view.

Sera were obtained from 28 professional prostitutes, aged 21–59. 21 sera from women (10 married and 11 single) aged 19–50 were used as controls. Frozen sections of unfixed normal adult testis were treated with the test sera, and then with rabbit antihuman γ-globulin fluorochromed with fluorescein isothiocyanate. The preparations were examined with a conventional microscope equipped with a dark-field condenser and illuminated by a high-pressure mercury-arc bulb (Reichert). The same labelled sera and optical arrangement have given good results in demonstrating lupus factor, antithyroid antibody,[4 6] and isoagglutinins A and B by the Szulman[7] method. We saw no evidence of selective staining of spermatids or other testicular elements by any of the sera.

These results might be interpreted in several ways:

(1) Immunisation to sperm is not a frequent cause of infertility in prostitutes, and presumably is an even less frequent cause of this disorder in other women.

(2) Immunity to sperm occurs with undetermined frequency in prostitutes, but is produced by cellular or delayed hypersensitivity rather than by circulating antibody.

(3) Such immunity is produced by circulating antibody which is not γ-globulin.

The prostitutes we talked to think that they are relatively infertile, considering their lack of contraceptive precautions in relation to their degree of exposure. The possibility of desensitisation by chronic exposure to large amounts of antigen has to be considered; but there has been no opportunity to study comparable sera after the donors had not been exposed as often as usual.

We should like to thank Mrs. Lois Adams, Mrs. Hazel Wilson, Dr. David Simon, and Mrs. Catherine Carroll for their help in collecting specimens and carrying out tests.

Children's Hospital Research Foundation, Departments of Pediatrics, Obstetrics, and Pathology, University of Cincinnati, Cincinnati, Ohio.

JAMES M. SUTHERLAND
BENJAMIN H. LANDING.

ASSESSMENT OF SKIN VIABILITY

Mr. MICHAEL N. TEMPEST writes:

"I would beg leave to correct the impression conveyed in your annotation of June 24 that I have been the leader of the team of workers in Chepstow using the intravenous dye technique in the assessment of skin viability.

"Along with other colleagues I have been intimately involved in this investigation from its beginning in the early

1. Cazal P., Isarn, P., Emberger, J. *Sang*, 1959, **30**, 1.

1. Rümke, Ph., Hellinga, G. *Amer. J. clin. Path.* 1959, **32**, 357.
2. *J. Amer. med. Ass.* 1921, **77**, 42.
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7. Szulman, A. E. *J. exp. Med.* 1960, **111**, 785.

part of 1955, but the prime mover and leader of this work is Mr. Emlyn Lewis, who has already demonstrated this technique to several scientific meetings in this country.

"The article of mine to which your annotation refers is the substance of a short paper given to the Association of Industrial Medical Officers in October last year."

Parliament

QUESTION TIME

Postgraduate Teaching Hospitals in London

Lady GAMMANS asked the Minister of Health whether he would make a statement on the future of the London postgraduate teaching hospitals.—Mr. ENOCH POWELL replied: Yes. Following consultations with the University of London, the British Postgraduate Medical Federation, and the University Grants Committee, I have agreed in principle that, in the interests of teaching and research and of the hospital service generally, the special postgraduate hospitals and institutes should as far as possible be brought together in two groups for which the nuclei already exist. Accordingly, I am proposing that the National Hospital for Nervous Diseases, the Hospital for Sick Children, the Royal National Throat, Nose, and Ear Hospital, and the Eastman Dental Hospital shall remain or be developed with their institutes on their present sites in the Holborn area; and the two branches of Moorfields Eye Hospital and the Institute of Ophthalmology will in due course be brought together and developed on the site of the Royal Free Hospital in Gray's Inn Road. As regards the other group, I am proposing that the Brompton Hospital (with which the London Chest Hospital is to be combined) and the Royal Marsden Hospital will remain and be developed with their respective institutes in their present locations on the Fulham Road. With them will be located the following smaller hospitals, with their institutes, as and when they are rebuilt: St. Peter's, St. Paul's, and St. Philip's Hospitals, St. John's Hospital for Diseases of the Skin, and also St. Mark's Hospital. Provision will be made for the eventual inclusion of the National Heart Hospital and the Institute of Cardiology. I am still considering the best arrangements to make for the town branch of the Royal National Orthopædic Hospital and its institute. Because of their special circumstances I have agreed that Queen Charlotte's Maternity Hospital and the Bethlem and Maudsley Hospitals, with their respective institutes, need not be moved into either of the two groups. Apart from the transfer of St. Mark's Hospital the proposals do not affect Hammersmith Hospital nor the Postgraduate Medical School associated with it. The proposals involve redevelopment of the sites now occupied by the Chelsea Hospital for Women and St. Luke's Hospital. The Chelsea Hospital for Women will be rebuilt adjacent to Queen Charlotte's. St. Luke's Hospital urgently needs to be replaced, and I am satisfied that satisfactory alternative geriatric provision can be made for the area; specific proposals will emerge from consideration of the 10-year plan for the South West Metropolitan Region.

Shortage of Hospital Pharmacists

Lord STONHAM asked H.M. Government whether they were aware that, owing to the acute shortage of pharmacists, hospitals throughout the country were unable to dispense prescriptions for a large proportion of patients; that, in particular, St. Thomas's Hospital had had to suspend dispensing for outpatients, and, since this involved a considerably increased cost to the Exchequer, what steps they were taking to improve the recruitment of hospital pharmacists.—Lord NEWTON replied: Hospital outpatient prescriptions are dispensed by retail chemists, and this is rarely because of staff shortage. St. Thomas's Hospital has temporarily closed its outpatient dispensary because several of the staff happened to leave simultaneously. The Board of Governors have been asked to reopen it as soon as possible. The shortage of pharmacists throughout the country affects retail business and industry as well as the hospital service. The salaries of hospital pharmacists were increased with effect from Jan. 1, 1960, by about 14%, and during 1960 the number of pharmacists in National Health Service hospitals increased from 1348 to 1444, the largest increase in a single year for several years.

Lord STONHAM: Is the noble Lord aware that at St. Thomas's 15,000 prescriptions per month will have to be sent to chemists, which will mean an extra cost to the Exchequer at the rate of £30,000 a year? Would it not be much better and much cheaper to pay hospital pharmacists salaries comparable to those paid by retail chemists, so that we can have pharmacists in hospitals?—Lord NEWTON: About 188 hospital authorities resort regularly to retail prescriptions, but in many cases only in detached clinics, such as child-guidance clinics, or in evening clinics where it would be inconvenient for patients to attend the hospital dispensary. About 700,000 retail prescription forms are used each year. This is a very small proportion of the total number dispensed. The new salary scales range from £690 to £1560 at the maximum, and many chief pharmacists receive additional allowances. There are now posts in the hospital pharmaceutical service which carry a total remuneration rising to £2000 or more a year. A claim submitted in May of this year to the appropriate Whitley Council for increases of 14–42% on the present salary scales is now being considered by the management side. Lord STONHAM: Would the noble lord convey to his right honourable friend that there is general uneasiness throughout the hospital world on this subject? With regard to St. Thomas's, their pharmaceutical department is working at half-strength and they may have to close some departments. It is no use building a £7 million hospital if you have not the staff to service the departments.—Lord NEWTON: I do not think it is quite true to say that St. Thomas's is now working at half-strength. What happened was that 5 out of 8 pharmacists in the basic grade left simultaneously at the beginning of June.

Retrospective Payments to Medical Teachers

Lord AMULREE asked H.M. Government what was the number of medical teachers employed by the universities who undertook clinical duties similar to their colleagues in the National Health Service and who were paid at similar rates, but who had, nevertheless, received back pay under the recommendations of the Royal Commission on Doctors' and Dentists' Remuneration only to Jan. 1, 1960, whereas their National Health Service colleagues had received such payments retrospective to March, 1957.—The EARL OF DUNDEE, Minister Without Portfolio, replied: There are 220 university medical teachers who received salaries corresponding to those approved for the National Health Service. All are professors, and I must make it clear that their salaries were not within the scope of the recommendations of the Royal Commission on National Health Service remuneration and I cannot therefore accept the comparison implied in the question. It was not considered right to make greater retrospective payments to these university teachers than to other university staff whose salaries were revised from Jan. 1, 1960, having regard particularly to the fact that university medical teachers in any case, because of their medical qualifications, receive higher salaries than other teachers.

Distinction Awards

Mr. CHRISTOPHER MAYHEW asked the Minister of Health if he was aware that in the recently published list of merit awards to consultants, 67% of neurologists received awards, and only 14% of mental health consultants; and by what criteria these awards were issued.—Mr. POWELL replied: Yes. The awards are made for professional distinction alone, on the advice of the Advisory Committee on Distinction Awards.

Group Practice Loans

The Minister of Health proposes to enable loans to be issued this financial year in England and Wales to a total of £430,000, which he estimates will be sufficient.

Children in Prison

Between Jan. 1 and May 31 this year 391 boys and 16 girls under seventeen were remanded to prison.

N.H.S. Prescriptions

During February, March, and April the number of items dispensed under the National Health Service was 22·2 million, 17·5 million, and 15·2 million.

Detention Centres Discharges

At the end of last year out of over 3600 boys released from detention centres in 1957–59, 55% had not been reconvicted. Of those who were first offenders, 74% had not been reconvicted.

Obituary

SAMUEL THOMPSON IRWIN

Kt, C.B.E., B.A., M.Ch. R.U.I., F.R.C.S.E., D.L.

Sir Samuel Irwin died on June 21 at his home in Belfast at the age of 84 years. He had spent the previous afternoon in the Northern Ireland Houses of Parliament, Stormont, where he had been a Unionist representative of Queen's University since 1948.

He was born in 1877 at Claudy, Co. Londonderry. He was educated at Foyle College, Londonderry, and at Queen's College, Belfast. In 1900, he graduated B.A. from the Royal University of Ireland and two years later he took his medical degree with honours. After holding resident posts in Belfast and St. Peter's Hospital, London, he was appointed in 1904 a surgical registrar at the Royal Victoria Hospital, Belfast. His surgical apprenticeship was long, for he was not elected to the staff of this hospital until 1918. But in 1911 he was appointed assistant surgeon to the Ulster Hospital for Women and Children, and it was here that his interest in orthopædic surgery developed. This was further stimulated by his service, during the 1914–18 war with the R.A.M.C., on the surgical staff of the Ulster Volunteer Force Hospital.

Although Irwin practised general surgery throughout his long life, his interest in orthopædics grew as the years passed. He was one of the oldest members of the British Orthopædic Association, a British member of La Société Internationale de Chirurgie Orthopédique et de Traumatologie, and vice-chairman of the Northern Ireland Council for Orthopædic Development from its inception in 1940.

After he retired from his hospital appointments he continued to serve the community. He was vice-chairman of the Northern Ireland Health Services Board, a member of the Northern Ireland Hospitals Authority, president of the Central Presbyterian Association, and a member of the Senate of Queen's University, to mention only a few of his activities. During the late war he was chairman of the Northern Ireland Medical War Committee, and in recognition of his services he was appointed C.B.E. in 1947. The following year he was elected to his parliamentary seat, and in 1957 he was knighted.

R. J. W. W. writes:

"In his younger days Sam Irwin was a keen cricketer and he played rugby for Ireland on nine occasions. He was a past president of the Irish Rugby Football Union and a past captain of the Royal Co. Down Golf Club. Many orthopædic surgeons will remember the wonderful party he gave there in 1948, when the British Orthopædic Association visited Belfast, and when the sailing of the Liverpool boat had to be postponed for some hours to fit in with his hospitality.

"He was a man of strong convictions, yet his quiet humour helped him to carry his years and his honours with humility and dignity. His greatest gift was undoubtedly his equanimity which was to stand him in good stead during the late war when his three sons were serving in the R.A.M.C., and especially when one of them was a prisoner-of-war. His reaction to all trials was characteristic—he simply took on more and more work, for he never doubted that 'we walk by faith and not by sight'."

Sir Samuel was a widower, and he leaves three sons and two daughters.

Mr. R. C. DAVENPORT

L. W. B. writes:

"It was with great confidence that one referred or took a patient to see Robert Davenport in consultation. Not only could the referring doctor be sure of an accurate, informative, and just full enough report and of well-considered and practicable advice, but it was certain that the patient, whether at hospital or consulting-room, would be kindly and patiently received and heard and given, not only instructions and advice, but the much rarer explanation of symptoms and answer to questions. '*What* a nice man!' said the returning patient, time and again, meaning 'this good, kind, thoughtful man has given me a full measure of his knowledge and skill and has inspired me with liking and trust'."

Public Health

Poliomyelitis

THE provisional number of new cases of poliomyelitis notified in England and Wales in the week ended June 17 was 20, of which 14 were paralytic. This brought the total for the first 24 weeks of the year to 235, of which 164 were paralytic. This total represents an increase of 68 cases over the total of 168 (108 paralytic) in the same period of 1960. The increase follows four years of steadily falling figures. Nearly all the cases now being notified are in patients who have not been immunised.

Diary of the Week

JULY 2 TO 8

Monday, 3rd

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. W. I. Card: Gastrointestinal Hormones.

Tuesday, 4th

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Brian Russell: Uncommon Skin Tumours.

Wednesday, 5th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Dr. Julius H. Comroe, Jr.: Pulmonary Circulation and Pulmonary Function. (Tudor Edwards lecture.)
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. H. J. Rogers: Penicillins and their Action on Cell Surfaces.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Recent Advances in the Study of Mycotic Infections.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. K. M. Citron: Asthma.
SOCIETY FOR ENDOCRINOLOGY
5.30 P.M. (26, Portland Place, W.1.) Sir Charles Dodds: Rime and Reason in Endocrinology.

Thursday, 6th

INSTITUTE OF CHILD HEALTH, THE HOSPITAL FOR SICK CHILDREN, Great Ormond Street, W.C.1.
5 P.M. Dr. Haddow H. Keith (Rochester, Minnesota): Use of Ketogenic Diet in Epilepsy in Children.

Appointments

East Anglian Regional Hospital Board:

ASIF, S. H., M.B. Punjab: registrar in psychiatry, Hellesdon Hospital, Norwich.
BARRETT, P. K. M., M.B. Lond., M.R.C.P.: senior registrar in chest medicine, Cambridge area chest clinic.
COWLE, J. B., M.D. Sydney: ophthalmic registrar, Norfolk and Norwich Hospital.
FRIDAY, E. P., M.B. Edin.: surgical registrar, Newmarket General Hospital.
GRAINGER, KENNETH, M.B. Lpool, F.F.R., D.M.R.D.: consultant radiologist, Ipswich and East Suffolk Hospital.
SAYANI, I. H., M.R.C.S.: orthopædic registrar, Norfolk and Norwich Hospital.
TROTTER, I. S., M.R.C.P.E.: consultant physician in geriatrics, West Norfolk and North Cambridgeshire area.

Notes and News

MENTAL HEALTH AND RELIGION

ON June 26, at a meeting in London organised by the National Association for Mental Health, the Churches' Council of Healing, and the Central Churches' Group of the National Council of Social Service, Rev. GEORGE C. ANDERSON, Director of the Academy of Religion and Mental Health in New York, spoke on Religion and Psychic Health. Mr. Anderson suggested that Christian religion may be on the verge of changes in theology as radical as those of the Protestant Reformation. Today psychiatry was compelling theologians to reexamine the nature of free will, human motivations, and the image of man.

In the United States clergymen had a special place in developing healthy emotional attitudes among children and adults. Clergymen were closely identified with worshippers at the time of deepest emotional significance in death, sickness, marriage, religious conversion. Unlike that of the psychiatrist, who was usually consulted only when a problem became intolerable, the pastor's door was always open.

But all too often clergymen were not aware of the impact of religious teachings and practices on emotional health. Certain religious beliefs and practices could hasten emotional illness. When the force of basic impulses was powerful, the taboos or morals of society might create an intolerable tension that could easily erupt into serious neurosis or psychosis. The heightening of guilt could be harmful physiologically and psychologically to one whose mental apparatus was already holding a full load of anxiety. Mental illness was often the price paid for being a civilised or a religious individual. The emotionally unstable were particularly vulnerable to certain religious beliefs. Rigid observance of religious devotions might be symptomatic of obsessional neurosis; and excessive penitence often revealed masochism.

Many churches in the United States had their own counselling services or centres; and some had large clinics staffed by physicians, psychiatrists, and psychologists. Some clergymen were spending up to half their time counselling. This could be dangerous unless they were given adequate knowledge of emotional health and illness. The lure of psychiatry was a temptation which clergymen should resist unless they were prepared to undergo intensive training in psychodynamics within the framework of their specific theology.

It was interesting to note, Mr. Anderson remarked, that Roman Catholic priests seemed to have better skills than Protestant clergymen in squaring psychiatric concepts with theology. Perhaps this resulted from better training in theology in the first place, but it was important for clergymen to understand that knowledge of mental health should be used to make them more effective clergymen and not pseudo-psychiatrists.

Problems like this had led Mr. Anderson, nearly six years ago, to create the Academy of Religion and Mental Health, which he conceived as a professional society, an educational institution, and a research organisation dealing with all relations between religion and health, and especially mental health. The idea quickly took hold and today over 3000 psychiatrists, physicians, psychologists, clergymen, sociologists, and a few cultural anthropologists were members. "By preparing our future clergymen, and by developing training programmes and seminars in villages and towns where priests, rabbis, and ministers are on the front line, the Academy has mobilised a massive attack on emotional and mental illness and strengthened the resources in preventive medicine and mental hygiene. . . . It is significant that nearly 10% of all the psychiatrists in the United States are members of the Academy of Religion and Mental Health. This does not mean that many psychiatrists are being converted to religion, but it does signify that they recognise that religion is an essential factor in health and they apparently seek closer collaboration with clergymen".

INSTITUTE FOR CARDIOVASCULAR RESEARCH, PRAGUE

ON June 9 a scientific conference was held in Prague to celebrate the 10th anniversary of this Institute for Cardiovascular Research. A number of communications, particularly on hypertension, nephritis, and atherosclerosis, reviewed the work that has brought it international recognition during the past decade, and an important new method for measuring blood-flow in vessels was described.

HELPING THE FAMILY

A LITTLE book [1] published by the Family Welfare Centre in Manchester for private circulation among doctors and social workers describes the history and development of the service, its present scope, and its future plans. The idea of starting a family welfare service came from Dr. Gertrude Jefferson (later Lady Jefferson), and she was its director until a year ago. While working in the maternity and child-welfare service in Manchester she realised the importance of the personal interest shown to mothers by the doctors and health visitors in the clinics. It often seemed to her that this was more important than the actual medical advice and what was needed was a family welfare service equipped to deal with psychological problems. In 1948 a centre was established and called the Family Welfare Centre. Its title was later regretted since its work has always been very much concerned with guidance; staffed by psychiatrists and psychiatric social workers, it is largely occupied in helping families to help themselves.

University of Oxford

Dr. C. Keith Simpson has been appointed university lecturer in forensic medicine, Dr. B. M. Mandelbrote clinical lecturer in psychiatry, and Dr. J. D. Morgan clinical lecturer in accident and orthopædic surgery.

University of London

Mr. H. J. B. Atkins, director of the department of surgery at Guy's Hospital and dean of the Institute of Basic Medical Sciences, has been appointed to the university chair of surgery at Guy's Hospital Medical School.

Mr. Hedley Atkins, who is 55 years of age, was educated at Rugby, Trinity College, Oxford, and Guy's Hospital. After qualifying in 1932 he held house-appointments at Guy's. He took the F.R.C.S. in 1934 and proceeded to the M.CH. Oxon. in 1936. The same year he was appointed a surgeon to Guy's. During the late war he served in the R.A.M.C. with the rank of lieut.-colonel. He is a member of the clinical research board of the Medical Research Council, of the General Medical Council, the Central Health Services Council, the council of the Royal College of Surgeons, and the executive committee of the British Empire Cancer Campaign. He is at present visiting Australasia as Sims travelling Commonwealth professor. He was made an hon. F.A.C.S. in 1957. His publications include *After Treatment* and many articles on cancer of the breast. He has also contributed to *French's Differential Diagnosis* and edited three series of *Tools of Biological Research*.

The title of reader in biology has been conferred on Dr. Agnes M. Hughes in respect of her post at the Royal Free Hospital School of Medicine.

University of Bristol

The degree of M.D. has been conferred on I. D. Fraser, Kathleen J. Harrison, and Timoleon Valaes and of PH.D. in the faculty of medicine on C. I. Phillips.

The degrees of M.B., CH.B. have been conferred on:

G. J. A. Brown, A. A. Brzechwa-Ajdukiewicz, Edith Creighton, B. H. Cummins, A. G. Morgan, J. A. Morphew, Violet A. Payne, Diana M. Young (second-class honours); D. W. R. Carr, Andreas Modestou Chrysaphinis, Marjorie A. Coutts, Aerona M. A. Crick, M. J. Crick, K. A. Day, Ayodele Babajide Olukoya Desalu, J. D. Egdell, I. F. Elliott, K. H. Gay, G. H. Gundy, C. P. Hallett, Barrie Hanstead, D. W. Hide, Eleanor J. A. Hughes, R. C. W. Hughes, Nkpanam Ikoku, W. A. Knight, J. M. McGarry, Vida V. Mungwira, A. S. Parker, R. F. Payne, M. F. Reed, R. R. Roy, A. K. Smeeton, T. D. Waterhouse, M. R. Watts.

1. Family Welfare Centre: an account of the work done in the Manchester Family Welfare Centre from its beginnings in 1948 to the present time when it has become a recognised branch of the Public Health Service. By NANCY E. LINGARD, psychiatric social worker, MARGARET PLATT, M.B., and BARBARA OLDHAM, M.B. Manchester: The Family Welfare Centre. For private circulation. 1961. Pp. 44. 5s. Obtainable from the Centre, Darbishire House, Upper Brook Street, Manchester, 13.

University of Leeds

The following degrees and diplomas have been conferred:

M.D.—M. S. Losowsky.

M.B., Ch.B.—D. J. Ashelford, Bryan Ballantyne, P. J. Bretherick, Jeffrey Ellis, Michael Klinger, J. K. Merritt, J. M. Raper, R. M. Riley, P. J. Smith, B. E. Walker, Pamela J. Walker, Syd Moy Wong.

D.P.H.—J. E. Lee.

University of Aberdeen

Mr. N. A. Matheson has been appointed to a lectureship in surgery, and Dr. P. W. Ross to a terminable lectureship in bacteriology.

University of Glasgow

Dr. E. M. McGirr has been appointed to the Muirhead chair of medicine in succession to Prof. L. J. Davis, who retires on Oct. 1.

Dr. McGirr, who qualified from the University of Glasgow in 1940, served with the R.A.M.C. for the next five years, spending the last three in the Far East, where he saw service in India, Burma, Siam, and Indo-China. On his return to Scotland he joined the Muirhead department of medicine in the Royal Infirmary, Glasgow, and was successively clinical assistant, lecturer, and (since 1952) senior lecturer. He received the degree of M.D. with honours last year and was awarded the Bellahouston medal. He was elected F.R.C.P. this year. His chief research interest has been in thyroid disease, and he has published papers on cretinism and juvenile myxœdema.

The following degrees and diplomas have been conferred:

M.D.—A. B. McL. Currie, G. L. Gibson, Maria A. Ratzer.

D.P.H.—Faramarz Adibzadeh, Marjory M. Buchanan, William Ducat, Nasser Fakhar, Emily A. Friel, F. C. Garry, P. J. Halket, Henry MacAnespie, Sarah C. McEwan, Jean M. McEwen, T. L. O'Donnell, S. G. Phillips.

Dr. J. F. Lamb has been appointed lecturer in physiology.

University of Wales

The degrees of M.B., B.CH. have been conferred on:

Hilda Bailey, V. A. Church, R. H. Clark, R. A. Cope, Deirdre J. Curran, D. M. Davies, H. S. Davies, J. S. Davies, Joan Evans, R. W. Fortt, Nancy E. Francis, Alfred Kwong Chun Hui, P. D. L. John, D. J. Jones, Helen W. Jones, Margaret E. Jones, Anne Kriescher, D. G. Lewis, C. C. McCormick, Wing Shang Ng, D. K. Peters, J. M. Peters, C. A. Quick, Jennifer H. Roberts, K. J. Russell, Patricia M. Wardlaw, J. G. Williams, N. B. Williams, A. C. MacD. Windsor, Brian Wookey.

Order of St. John of Jerusalem

The Queen has sanctioned the following promotions in, and appointments to, this order:

As Commanders.—Surgeon Rear-Admiral W. V. Beach, O.B.E., F.R.C.S.E., Q.H.S., Surgeon Rear-Admiral J. M. Reese, O.B.E., M.R.C.S., Q.H.P., Major-General H. E. Knott, C.B., O.B.E., M.D. Q.H.P.

As Officers.—Surgeon Captain E. D. Caldwell, M.D., M.R.C.P., R.N., A. J. Struthers, M.B., W. T. Currie, M.B., W. J. Collins, M.B., F. M. Hanna, B.A., M.B., F.R.C.S., G. J. Romanes, M.A., M.R.C.S., James Dobson, M.B., Surgeon Captain M. H. Adams, M.B., R.N., Lieut.-Colonel W. R. Lamb, M.C., M.B., Major R. M. Gibson, M.D., F.R.C.S., Colonel Elston Grey-Turner, M.C., T.D., M.R.C.S., Q.H.P., Margaret F. Gillison, M.B.

Faculty of Radiologists

The following officers have been elected for 1961–62:

President: Dr. Rohan Williams, vice-presidents: Dr. Eric Samuel and Dr. R. C. Tudway, warden of the fellowship: Prof. R. McWhirter, hon. treasurer: Dr. E. C. Easson, hon. secretary: Dr. C. J. Hodson, hon. editor: Dr. David Sutton.

British Association of Urological Surgeons

The following have been elected officers and members of council for 1961-62:

President, Prof. L. N. Pyrah; immediate past president, Mr. David Band; vice-president, Prof. V. W. Dix; hon. treasurer, Mr. R. A. Mogg; hon. secretary, Mr. D. Innes Williams; hon. editorial secretary, Mr. J. D. Fergusson; members of council, Mr. G. H. Baines, Mr. S. H. C. Clarke, Mr. J. P. Mitchell, Mr. T. Moore, Mr. B. H. Page, Mr. F. P. Raper, Mr. W. Barr Stirling, Mr. G. C. Tresidder, Mr. W. K. Yeates.

British Medical Association

The Association is to make awards of the C. H. Milburn, Doris Odlum, Nathaniel Bishop Harman, Brackenbury, Sir Charles Hastings, and Charles Oliver Hawthorne prizes. Essay prizes for medical students and provisionally registered practitioners, research scholarships, and medals and certificates for 16mm. medical films are also offered. Further particulars may be had from the secretary of the Association, Tavistock Square, London, W.C.1.

International Union of Railway Medical Services

This Union is to hold a congress from Sept. 5 to 9 in Istanbul, when the main subject for discussion will be medical standards for staff. Those giving papers will include Dr. F. A. Watkins and Dr. J. S. Grant.

Congress of Anæsthesia in Belgium

The first Belgian congress of anæsthesia is to be held in conjunction with the third congress of the Association of European Anæsthetists from Oct. 5 to 8 in Namur. Further particulars may be had from the secretary Dr. J. de Ville de Goyet, 3, Avenue de la Vecquée, Namur.

Society of Medical Officers of Health

This society is to hold a refresher course for county district medical officers of health from Sept. 21 to 23 at the London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1. Further particulars may be had from the organising secretary, Dr. J. H. Hudson, White Oak, Swanley, Kent.

British Academy of Forensic Sciences

The annual scientific meeting of this Academy will be held in London on Saturday and Sunday, July 15 and 16, when the main theme will be Crime—Responsibility, Investigation, and Treatment. Cards of admission may be had from the secretary, 28, Portland Place, London, W.1.

Chest and Heart Association

A health conference for executives is to be held by this Association on Nov. 30, at 10 A.M., at Connaught Rooms, Great Queen Street, London, W.C.2. The speakers will be Sir Derrick Dunlop, Dr. J. F. Loutit, Dr. Annis Gillie, Dr. Alec Lerner, Sir Cecil Wakeley, Prof. A. W. Woodruff, Sir Charles Dodds, and Dr. H. Guy Dain. Further particulars may be had from the Association, Tavistock House North, Tavistock Square, W.C.1.

National Fund for Research into Poliomyelitis

This fund has announced grants totalling £36,400, including the following:

£10,000 to King's College, Newcastle upon Tyne (University of Durham) for a comprehensive survey of neurological morbidity in the city of Carlisle (under the direction of Dr. Henry Miller); £5650 to the Royal Free Hospital School of Medicine, London, to establish a mobile neurophysiological research unit for the study of patients with acute encephalitis (under the direction of Dr. G. Pampiglione); £4700 to the department of microbiology, Queen's University of Belfast for a research fellowship in virology; £5650 to the National Spinal Injuries Centre, Stoke Mandeville Hospital, Bucks, for a physiological study of the effects of physical exercise on patients with injury or disease of the spinal cord; and £4800 to the department of pathology, Cambridge University, for the study of the natural history of virus diseases seen in general practice, particularly those of the respiratory tract.

Colonel H. A. Mullen has been appointed honorary physician to the Queen in succession to Colonel J. H. Prain and Colonel G. A. W. Neill honorary surgeon to the Queen in succession to Colonel R. G. W. Ollerenshaw.

The proceedings of the symposium of the British Society for Immunology on immunity to protozoa (*Lancet*, 17 June, 1961, p. 1343) are to be published early next year under the editorship of Prof. P. C. C. Garnham by Blackwell Scientific Publications, Oxford.

The Nurses (Amendment) Act came into force on June 29, and in future "enrolled assistant nurses" will be entitled to call themselves "enrolled nurses" and to add after their names the initials S.E.N.

N.A.M.H. Guide to the Mental Health Act 1959—This booklet summarises the main provisions of the Act, indicates the changes which it has made, and briefly describes the new administrative machinery which it sets up. Copies (2*s.* 6*d.*, 2*s.* 8*d.* post free) may be had from the National Association for Mental Health, 39, Queen Anne Street, London, W.1.

CORRIGENDUM: *Spironolactone Therapy in Hypokalæmia.*—In Dr. Bauer and Dr. Telfer's letter last week, the figure for total exchangeable potassium after spironolactone in the 49-year-old man should have been 43·6 mEq. per kg. and not 34·6.